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56-61.- RENAL FUNCTIONAL EQUATIONS: THEIR EVOLUTION AND ROLE IN CKD PATIENTS

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Editorial:

ENVEJECIMIENTO

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English Version

El envejecimiento de la población será en los próximos años un importante problema de salud[1].

Hay que señalar que los cambios relacionados con el envejecimiento, son variables en los diferentes individuos y no van paralelos a la edad cronológica. Así, la determinación de la edad fisiológica permite un mejor conocimiento del riesgo de mortalidad, de la valoración de la susceptibilidad al estrés y de la dependencia funcional[2,3].

La Valoración Geriátrica Integral (VGI), incluye el análisis de la situación física, la morbilidad, el estado nutricional, los síndromes geriátricos y el soporte social, siendo el instrumento mejor validado para este propósito.

Se trata de un proceso diagnóstico multidimensional e interdisciplinario, para determinar las capacidades médicas, psicológicas y funcionales de un anciano frágil con el fin de desarrollar un plan coordinado e integrado para el tratamiento y seguimiento a largo plazo. Hace hincapié en la calidad de vida y estado funcional. La Valoración Geriátrica Integral es un proceso dinámico, ya que se realiza repetidas veces a lo largo del tiempo, para constatar la evolución del paciente y evaluar las medidas terapéuticas aplicadas. Su

objetivo es elaborar un plan integral, individualizado, diagnóstico, terapéutico y de seguimiento[4].

Como características comprende, el empleo de equipos interdisciplinarios y de instrumentos estandarizados[5].

Una de las metas del tratamiento en personas mayores es la prolongación de la esperanza de vida "activa", que implica que además de curar se consiga una prolongación de la vida junto con el tratamiento paliativo de los síntomas.

Un problema especial relacionado con el manejo de los pacientes mayores es la presentación de enfermedades intercurrentes y las interacciones farmacológicas entre los fármacos que se pautan como tratamiento de las mismas[6]. La gestión de la complejidad es la principal habilidad de los cuidados médicos de pacientes mayores, debiendo basarse la elección del tratamiento en datos objetivos[7].

En el año 2011, en España, el cáncer fue la segunda causa de muerte en la población general y en los mayores de 79 años; entre 40 y 79 años, fueron los tumores la primera causa de muerte[8]. Debido al envejecimiento de la población, previsiblemente la incidencia de cáncer aumentará en los próximos años.

El impacto de la Valoración Geriátrica Integral en el marco de la oncología geriátrica, no está claramente definido pero es muy recomendable implementarla antes de tomar una decisión sobre el tratamiento en pacientes con cáncer y edad avanzada[9].

La International Society of Geriatric Oncology Chemotherapy ha elaborado varias guías para mejorar el tratamiento y los cuidados en pacientes ancianos con cáncer, lo que facilita la toma de decisiones por parte de los profesionales[10].

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Editorial:

AGING

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Version en español

The aging of the population will be a significant health problem in the coming years[1].

It has to be pointed out that the changes associated with aging are variable in different individuals, and may not be parallel with that of chronological age. Thus, the determination of physiological age gives a better knowledge of mortality risk, by evaluating the susceptibility to stress and functional dependence[2,3].

The Comprehensive Geriatric Assessment (CGA), includes the analysis of the physical status, morbidity, nutritional state, geriatric syndromes, and social support, and is the best validated tool for this purpose.

It is a multidimensional and multidisciplinary diagnostic process, to determine the medical, physiological and functional capacities of a fragile elderly person, with the aim of developing a coordinated and comprehensive plan for long-term treatment and follow-up. It emphasises the quality of life and functional status. The Comprehensive Geriatric Assessment is a dynamic process, since it is performed repeatedly over time to establish the progress of the patient and to assess the therapeutic measures applied. Its aim is the

preparation of a comprehensive, individualised, diagnostic, therapeutic and follow-up plan[4].

Its main features are, the use of interdisciplinary teams and standardised assessment tools[5].

One of the aims of the treatment in the elderly is to extend the "active" life expectancy, which involves, besides curing, an increase in life-span, along with palliative treatment of the symptoms.

One particular problem associated with the management of elderly patients is the presence of intercurrent diseases, and pharmacological interactions between the drugs prescribed for the treatment of these diseases[6]. The management of the complexity is the main skill in the medical care of the elderly, with the choice of treatment being based on objective data[7].

In 2011, cancer was the second cause of death in the general population and in people over 79 years in Spain, with tumours being the first cause of death between 40 and 79 years[8]. Due to the aging of the population, it is likely that cancer incidence will increase in the coming years.

The impact of the Comprehensive Geriatric Assessment within the framework of geriatric oncology is not clearly defined, but it is highly recommended to implement it before making a decision on the treatment in patients with cancer and advanced age[9].

The International Society of Geriatric Oncology Chemotherapy has prepared several guidelines to improve the treatment and care in elderly patients with cancer, which may help health care professionals in the decision-making process[10].

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UTERINE ARTERY EMBOLIZATION FOR THE TREATMENT OF UTERINE FIBROIDS.

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ABSTRACT

AIM: To determine the outcome of uterine artery embolization in patients with symptomatic uterine fibroids, in order to assess the response of symptoms and fibroid size.

METHODS: We analyzed the results of a population study of 112 patients with uterine fibroids made in the period between 2006 and 2010. Main parameters were assessed improvement or disappearance of symptoms and downsizing the adverse effects of the procedure.

RESULTS: The predominant age of the patients are in the group of 41-45 years with 80.35%, being the most common symptom of menorrhagia 66.07%, myoma volume ranged between 35cm^3 and 523cm^3, and procedure duration ranged from 1 hour to 2.5 hours. The most common symptoms after embolization was mild pain 44.64%, not having symptoms in 43.75%. Also it was associated nausea in 8.03% and vomiting in 3.57% as other adverse effects. After three months of treatment 47.32% had oligomenorrhea and amenorrhea was 17.85%. Fibroid size at 6 months was reduced significantly dominate the volume between 36 and 113cm^3.

CONCLUSION: Uterine artery embolization is an effective treatment for symptomatic fibroids, considered an alternative to surgical treatment.

Key words: syntomatic myomas, leiomiomas, uterine artery embolization.

RESUMEN: EMBOLIZACIÓN DE LAS ARTERIAS UTERINAS PARA EL TRATAMIENTO DE FIBROMAS UTERINOS.

OBJETIVO: determinar el resultado de embolización de la arteria uterina en pacientes con fibromas uterinos sintomáticos, con el fin de valorar la respuesta de los síntomas y el tamaño de los miomas.

MÉTODOS: Se analizaron los resultados de un estudio que incluye 112 pacientes con fibromas uterinos, estudiadas y tratadas en el periodo entre el año 2006 y 2010. Los parámetros principales evaluados fueron: la mejoría o desaparición de los síntomas, la reducción del tamaño y los efectos adversos del procedimiento.

RESULTADOS: La edad predominante de las pacientes está en el grupo de 41-45 años representando el 80,35%, y siendo el síntoma más común la menorragia, presente en el 66,07% de las mujeres incluidas en el estudio. El volumen de los miomas osciló entre 35cc y 523cc, y la duración del procedimiento fue de 1 hora a 2,5 horas. El síntoma más común después de la embolización, consistió en un dolor leve referido por el 44,64% de las mujeres, frente a un 43,75% que permanecieron asintomáticas. También se registraron náuseas y vómitos en el 8,03% y en el 3,57% respectivamente, como efectos adversos al procedimiento. Transcurridos tres meses del tratamiento, el 47,32% presentaron oligomenorrea y un 17,85% amenorrea. El tamaño del mioma a los 6 meses tras la embolización de la arteria uterina se redujo de forma significativa, disminuyendo el volumen entre 36 y 113cc.

CONCLUSIONES: La embolización de la arteria uterina es un tratamiento efectivo para los miomas sintomáticos, representando una alternativa al tratamiento quirúrgico. Palabras clave: miomas sintomáticos, leiomiomas, embolización de la arteria uterina

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INTRODUCTION

Uterine fibroids, or myomas, are tumours of the smooth muscle layer of the uterus, which appear in approximately 25% of all fertile women. Although some of these fibroids are asymptomatic, more than 50% of them cause symptoms that require treatment. Some of the most common symptoms are metrorrhagia, anemia or compressive symptoms, such as pain or mass effect, which also have a large influence on fertility[1].

Treatment of fibroids presents several alternatives, from medical treatments with hormones (levonorgestrel) and gonadotropin-releasing hormone analogues (GnRH analogues), to surgical treatments, which have been for many years the most used therapeutic approach. The most commonly techniques used were hysterectomy or myomectomy, either by laparotomy or laparoscopy, together with the hysteroscopic resection of the fibroid[2]. However, the combination of risks associated to surgical treatments and the effects that surgery sometimes has on young women, which can sometimes affect or hinder fertility, together with the fact that patients wish to avoid surgery[3] have led to the search of alternatives for surgical approaches. Embolization appears as an alternative for traditional therapies for patients with symptomatic fibroids.

This approach is adequate in premenopausal patients who wish to avoid hysterectomy or who present medical contraindications for surgery[4]. Ravina[5] initially developed the embolization of fibroids in France. Afterwards, in 1997, the results for patients treated in the USA were published[6].

Our objective is to present the results of uterine artery embolization on women with symptomatic uterine fibroids.

MATERIAL AND METHODS

Observational, multi-center and retrospective study.

Study population:

We analyzed the results of 112 uterine artery embolization procedures carried out in the Unit of Interventional Radiology of the University Hospital of Salamanca on patients who were transferred from the external consultations of the Department of Gynecology and also from other centers, who were diagnosed with intramural uterine fibroids and presented symptoms such as metrorrhagia, anemia and/or mass effect. Patients who were allergic to iodinated contrasts were excluded from the study.

Exclusion criteria were fibroid tumors of more than 12 cm, subserosal fibroids and submucosal fibroids. Desire for fertility was a partial exclusion criterion. Before the embolization, a Nuclear Magnetic Resonance (NMR) was performed in order to define

the location, size and number of tumors. Analysis, pregnancy test and hormonal study were also carried out.

All the patients received written information about the treatment they would undergo, together with its alternatives and the informed consent form.

Procedure

All patients were scheduled for hospitalization. Urinary catheterization and the insertion of a peripheral intravenous catheter were established as compulsory steps before the procedure.

Analgesia was provided by the Department of Anaesthetics with the insertion of an epidural analgesia catheter that was kept for at least 24 hours. Antibiotic prophylaxis with cefazolin 2g was also provided one hour before the procedure.

The most common approach for the uterine artery embolization is the right common femoral artery. The procedure generally starts with the Seldinger technique (the needle and the guide-wire are placed in the sheath and the catheters pass through it). The common femoral artery is punctured, generally on the right side, but in some cases also bilaterally, with an Abbocath catheter 18G and a 0.35" radioscopically guided hydrophilic guide-wire. Then, the 4-F or 5-F size Cobra, Multipurpose and reverse Simmons selective catheters pass through it, with a cross-over and Waltman loop technique for the corresponding catheters of the hypogastric artery and the identification of the uterine arteries from both sides, with the adequate radiological projections. In some cases, an aortoiliac angiography with a pigtail catheter is performed before this stage, but it increases the exploration time and the radiation dose. It is advisable to leave the 4-F or 5-F catheter in the hypogastric artery and to use road-mapping for the catheterization, with a coaxial micro-guide and a 3-F micro-catheter in the uterine artery, in order to avoid spasms that would prevent embolization. The catheters will surpass the point of exit of the cervico-vaginal arteries.

Once in the last horizontal or ascending portion of the uterine artery, 1-3cm syringes are used to administer antegrade injections of PVA (polyvinyl alcohol) particles of 300-500 microns and then 500-700 microns, or embospheres of 500-700 and 700-900 microns, pre-loaded with physiological saline solution and contrasts with a medium concentration of 50%. Our objective is to close the arterial input of the fibroid, because its tissue is highly sensitive to ischemia. Thus, we can maintain a normal endometrial and myometrial vascularization, that is, the vessels of the perifibroid plexus are occluded while the uterine perfusion is maintained.

The end-point is randomly determined after the fibroma is devascularized, with a retrograde flow towards the internal iliac artery or a slow antegrade pump flow of 5 beats.

At the end, the common femoral artery is compressed by hand, or sealed with devices for percutaneous closure.

During the procedure, some radioprotection measures were applied, such as a minimal magnification, the collimation of the fluoroscopic image, short series of images per second and anteroposterior projection. The monitoring of a potential post-embolization syndrome is carried out in the recovery room and in the section of gynecology. The monitoring process lasted for 24-48 hours.

Statistical study

The clinical characteristics were evaluated statistically by use of the Fisher's exact or Chi-square test with linear by linear association. Statistical analyses were undertaken using SPSS software (version 18). A P-value <0.05 was considered statistically significant.

RESULTS

The age of the patients ranged between 29 and 50 years. The 29-year-old patient presented a 10cm fibroid tumor, and she wanted to keep her uterus, so she asked for an embolization, because surgery involved a myomectomy and it could not guarantee its integrity. Two patients included in the group between 31 and 35 years old also wanted to keep their uteruses intact. The largest group included patients between 41 and 45 years, with 90 patients (80.36%), followed by the group of patients between 46 and 50 years (16 patients, 14.28%). They all met the criteria for embolization. The main symptom for consultation was menstrual alterations with menorrhagia (66.07%), followed by metrorrhagia (19.65%) and polymenorrhagia (14.28%). All the patients presented anemia and had a long-duration treatment for iron deficiency. They all underwent an ultrasound study in which the presence of one or more fibroids was established (Table 1).

Table 1. Patients characteristics

	Patients (n = 112)	Percentage (%)
AGE		
≤ 30	1	0.89
31-35	2	1.79
36-40	3	2.68
41-45	90	80.36*
46-50	16	14.28
CURRENT SYMPTOMS		
Polymenorrhagia	16	14.28
Menorrhagia	74	66.07*
Metrorrhagia	22	19.65
NUMBER OF FIBROIDS		
Isolated	48	42.86*
2	26	23.21
3	22	19.65
Multiple (>3)	16	14.28

*p < 0,05

There was a single tumour in 42.86%; 23.21% presented two tumors; 19.65% presented three tumours; and 14.28% had a polyfibroid uterus. The volume of the fibroids was confirmed by NMR and it ranged between ≤35cm^3 and 523 cm^3. In 8.03%, the fibroids reached a volume of 268cm^3 and 523 cm^3, while the tumors most commonly subject to embolization had a volume between 114cm^3 and 267cm^3 in 55.35% of the treated fibroids. In 27.7%, the fibroids had a volume between 36 cm^3 and 113 cm^3, and 8.92% had fibroids of less than 35cm^3 (Table 2).

Table 2. Fibroids volume.

	Patients N = 112	Percentage (%)
FIBROIDS VOLUME: before treatment (cm^3)		
≤ 35 (≤ 4cm maximum diameter)	10	8.92
36-113 (4,1- ≤ 6cm maximum diameter)	31	27.7
114-267 (6,1- ≤ 8cm maximum diameter)	62	55.35*
268-523 (8,1- ≤ 10cm maximum diameter)	9	8.03
FIBROIDS VOLUME: 6 months after treatment (cm^3)		
≤ 35 (≤ 4cm maximum diameter)	32	28.57
36-113 (4,1- ≤ 6cm maximum diameter)	56	50*
114-267 (6,1- ≤ 8cm maximum diameter)	21	18.75
268-523 (8,1- ≤ 10cm maximum diameter)	1	0.89
No myoma	2	1.79

*$p < 0,05$

The duration of the embolization procedure was highly variable, depending on multiple factors, such as size, location and the presence of cesarean scars or scars due to other type of operations, ranging from 2 hours (>1.5 - ≤2h) (8.93%), to 1 hour 30 minutes (>1 - ≤1.5h) (60.71%) and to 1 hour (≤1h) (26.79%).

The uterine artery embolization involves the appearance of ischemia, which manifests itself as pain. All the patients were treated with analgesia, via a catheter for the first 24 hours, and then with intravenous and oral analgesia. The pain was hard in 4.46%, moderate in 7.14% and mild in 44.64%. 43.76% did not present any pain.

Apart from pain, other types of clinical alterations can appear during the immediate period after embolization. The most important one was abdominal bloating or distension (18.75%), nausea (8.03%) and vomiting (3.57%). 67.87% did not present any of these symptoms.

Six months after embolization, menstruations had changed in all cases. 47.32% presented oligomenorrhea; 34.82% presented normal menstruation (eumenorrhea); and 17.86% presented amenorrhea, which could be helped by the age of the patient, her hormonal condition and the size of the fibroid tumor. (Table 3).

Table 3. Uterine artery embolization time and post procedure characteristics.

	Patient N = 112	Percentage (%)
PROCEDURE TIME (hours)		
≤ 1	30	26.79
>1 - ≤ 1.5	68	60.71*
> 1.5 - ≤ 2	10	8.93
> 2 - ≤ 2.5	4	3.57
POSTPROCEDURE ANALGESIA		
Epidural	69	61.60
Epidural + Analgesia e.v.	43	38.40
POSTPROCEDURE SYMPTOMS		
Mild pain	50	44.64
Moderate pain	8	7.14
Hard pain	5	46
No symptoms	49	43.76
OTHER POSTPROCEDURE ADVERSE EVENTS		
Nausea	9	8.03
Vomits	4	3.57
Abdominal bloating	21	18.75
Hematoma	2	1.78
No symptoms	76	67.87*
CLINICAL STATUS 3 months after treatment		
Oligoamenorrhea	53	47.32*
Eumenorrhea	39	34.82
Amenorrhea	20	17.86

*p < 0,05

Six months after embolization, the volume of the tumor had been reduced at different degrees. In 28.57% of the patients, it was equal to or smaller than 35cm^3; in 50% of the patients, the volume was between 36cm^3 and 113cm^3; and in 19.04% of the patients, it had become calcified. Table 2.

Analgesia was provided with catheter along in 61.60%, and with catheter plus intravenous analgesia in 38.40%.

DISCUSSION

The use of an alternative technique to surgery with a lower morbidity and shorter hospital stays represents a significant medical advance, because women who do not wish to undergo a hysterectomy for a fibroid tumor have now access to different less-invasive alternatives[7].

The embolization technique involves a selective blockade of the blood flow of the vessels of the fibroid with embolic agents through catheters. These embolic agents can be classified into different types[8, 9, 10], and the literature does not describe any problems related to any possible reactions they might cause. The insertion of catheters does not require general anesthesia, and it can be done with local anesthesia and a mild sedation[11], although the insertion of an epidural catheter allows for a proper analgesia and the control of pain after the embolization.

The size of the fibroids that underwent embolization was variable, although they were usually of less than 10 cm. The effectiveness of the embolization of giant fibromas has been assessed, and a total reduction has been observed in 42.9% of the cases[12]. The results described after embolization are very similar.

It was evaluated efficacy of embolization of the uterine arteries in uterine myomas depending on peculiarities of the blood flow in the system of the uterine arteries reports very positive results, and in the points out a prolonged irritation of the puncture site as the most common adverse effect reported by the patients[13]. The most favorable finding was the immediate remission of the symptoms. Sone[10] reports the remission of menorrhagia in 90% of the cases, of the pelvic pain in 78% of the cases, of the general symptoms in 98% of the cases and a reduction of the volume of the fibroid after 12 months in 61% of the cases. He used gelatin sponge for the embolization. A comparative study[14] was carried out with 375 patients with symptomatic fibroids who underwent different treatments (embolization, myomectomy and hysterectomy). 12 months after treatment, the three procedures had resolved the symptoms, and hysterectomy was the most effective approach for the resolution of the clinical disorder. Embolization was the technique with the best recovery rates regarding time and low morbidity. Apart from the symptoms, the reduction of the size of the uterine fibromas is another important aspect to be taken into account. A study reports a volume reduction of 50% after one year and all patients were asymptomatic[15].

One of the circumstances to be considered is the state of the endometrium and the uterine muscle. The NMR revealed a transient ischemia of the uterus which involved the endometrium and the lower and middle part of the myometrium of the uterine body and the fundus of the uterus. However, no alterations are found in the cervix and the subserosal tissue. In most cases, the myometrial tissue recovers completely after 48-72 hours, while the fibroid tumor suffers an irreversible infarction due to the ischemia[16]. In the diagnosis of fibroids and the monitoring after embolization, ultrasounds and NMR can be safe and reliable techniques. However, comparative studies have revealed some differences in the volume of the tumors between both techniques and NMR has been more effective in the characterization of fibroids[16, 17], and the monitoring after embolization can be carried out with ultrasounds[18].

Possibly, one of the problems derived from the different treatments of fibroid tumors can be due to the choice of the technique. Therefore, the alternatives for any single approach must be also taken into account. A study assessed the response after 5 years for two randomly distributed groups of patients who underwent hysterectomy and embolization. In the patients who underwent embolization, 24.7% had also underwent a hysterectomy because the symptoms had not completely disappeared, which reveals that embolization can be an alternative for hysterectomy and, with a proper selection of indications, can produce very positive results. For this reason, it is crucial to adequately select the patients and to define the location and size of the tumor, which are essential factors for good results[19]. A study compared the effectiveness, feasibility and morbidity rates of preoperative embolization or ligature of the uterine arteries in the preparation for conservative surgery of uterine fibroids, in which the choice of approach depends on the amount, size and topography of the fibromas[20]. These techniques are effective in the reduction of bleeding and they are compatible with fertility. With regard to the adverse effects they can present, a study shows the appearance of pre-menopausal symptoms or the appearance of menopause[21] and the spontaneous vaginal expulsion of the fibroid[22].

There are some doubts about the possibility that patients who underwent an embolization may present ovarian cancer, but at the present moment there are no published studies or references on the subject[23]. However, one case of advanced ovarian carcinoma after an embolization has been described[24].

The most complex situation derived from embolization is the preservation of fertility. There are few publications related to the problems of pregnancy after embolization, although they indicate that some of the pregnancies go on to term, albeit with an increased number of miscarriages and preterm deliveries. A study that monitored 100 patients who underwent embolization with tris-acryl gelatin microspheres detected 11 pregnancies (19.2%) of all patients who wished to preserve their fertility), with 8 live birth (4 of them with vaginal birth and 4 of them with a Cesarean section). Gestation lasted for approximately 37 weeks and none of the fetuses showed chromosomal abnormalities. No abnormal placental implantations were observed[25]. However, a study showed the appearance of placenta accreta in women who underwent embolization of a fibroid tumor and got pregnant afterwards[26].

As a conclusion, the embolization of the fibroid tumor can be an effective alternative for the resolution of symptoms (particularly anemia) caused by these benign tumors without the need of surgery.

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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST: The authors declare that there is no conflict of interest in the present study

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Comment of the reviewer Dra. Beatriz Cuevas Ruiz MD. PhD.Servicio de Hematología y Hemoterapia. Hospital Universitario de Burgos. Spain

The procedure for uterine artery embolization, permits treatment of fibroids fitness for repair not. The ease and simplicity of the technique make it an accepted therapeutic option for patients who undergo surgery.

The study shows an improvement of symptoms caused by uterine myoma as metrorrhagia and anemia, and reduced fibroid size.

Even though the desire for fertility was partially exclusion criteria for this study, relieves literature review the possibility of pregnancy following uterine artery embolization is comparable to that of the general population, although studies of patients subjected to this technique have a higher incidence of spontaneous abortions.

Comment of the reviewer Carlos G. Musso, MD. PhD. Ageing Biology Unit. Hospital Italiano de Buenos Aires. Argentina

This article clearly describes the potential advantages and disadvantages that the process of uterine artery embolization has in the treatment of uterine fibroid entity which is the most common gynecological tumor and usually become symptomatic in about 50% of women who suffer it. Among these symptoms are metrorrhagia, anemia (submucosal location), urinary frequency, constipation, bladder and / or ureteral compression (subserosa location), among others.

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URINARY INCONTINENCE: KNOWLEDGE, ATTITUDES, AND PREVALENCE AMONG OLDER ARGENTINE FEMALES.

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Comment of the reviewer Dr. Alberto Enrique D'Ottavio. **Professor and researcher. Facultad de Ciencias Médicas and Consejo de Investigaciones. Universidad Nacional de Rosario. Rosario, Argentina.**

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SUMMARY:
Objectives: This study aimed to investigate the knowledge and attitudes of Argentine women 65 years of age and older regarding urinary incontinence (UI).
Methods: A cross-sectional study of 238 community-dwelling Argentine women 65 years of age and older was conducted in San Justo, Argentina. Data were collected by in-person interviews.
Results: Regarding knowledge, 232 (97.5%) of the women surveyed were familiar with the term urinary incontinence, but 152 (63.9%) falsely believed that UI is a normal part of aging and 163 (68.5%) did not know about pelvic exercises or a surgical option to treat UI. A total of 106 (44.5%) women reported symptoms of UI.
Discussion: Older Argentine women are misinformed about UI. Interventions are necessary to increase their knowledge and healthcare seeking behaviors.

KEYWORDS: Argentine women. Urinary incontinence. Knowledge. Treatment. Geriatric.

RESUMEN: Objetivo: Este estudio tuvo como objetivo investigar el conocimiento y las actitudes de las mujeres argentinas de edad mayor o igual a 65 años respecto de la incontinencia urinaria (IU).

Método: Se realizó un estudio transversal de 238 mujeres de edad mayor o igual a 65 años residentes de la ciudad de San Justo, Argentina. Los datos fueron recolectados a través de entrevistas personales.

Resultados: 232 de las mujeres entrevistadas (97.5%) estaban familiarizadas con el término de IU, pero 152 (68.5%) creían erróneamente que la IU era parte normal del envejecimiento y 163 (68.5%) no sabía acerca de los ejercicios pélvicos o una opción de tratamiento quirúrgico.

Conclusión: Las mujeres argentinas de edad mayor o igual a 65 años que habitan en la ciudad de San Justo, están mal

informadas respecto de la IU, de modo que intervenciones son necesarias a fin de aumentar su conocimiento sobre el tema a fin de que tengan acceso a una mejor atención médica.

PALABRAS CLAVE: Mujeres argentinas. Incontinencia urinaria. Conocimiento. Tratamiento. Geriatría

INTRODUCTION

Urinary incontinence (UI) is a significant health problem that affects an estimated 200 million adult women worldwide[1]. Urinary incontinence, as defined by the International Continence Society Committee, is the "complaint of any involuntary leakage of urine"[2]. The effects of UI, especially amongst older women, can be debilitating physically, psychologically, and socially [3].

Studies have shown that most women with incontinence can be successfully treated by simple and effective methods[4]. However, the less women know about the symptoms, causes, and treatments of UI, the less likely they are to seek help[5]. Proper management of the condition by both healthcare professionals and community workers is dependent on women's attitudes and knowledge about UI[4]. It is likely that improving a woman's knowledge about UI will increase her healthcare seeking behaviors and the possibility of receiving effective treatment[6].

Therefore, it is crucial to determine what women actually know about UI. Previous research has found Hispanic women to have a higher prevalence of UI compared to white, black, and Asian American women[7]. However, to the best of our knowledge, no data exist about UI knowledge and prevalence specific to older Argentine women.

The present study was conducted to answer the following questions: (1) What do community-dwelling Argentine women 65 years of age and older, regardless of their current UI status, know about UI? and (2) What is the prevalence of UI in a randomly selected sample of older Argentine women in our Hospital programmatic area?

MATERIAL AND METHODS.

Study Setting and Sample Assembly

This cross-sectional study was conducted between September 2009 and December 2009 at the Hospital Italiano (HI) de Buenos Aires in San Justo, Argentina. HI is a community-based, academically affiliated, out-patient and in-patient multi-specialty hospital. The out-patient clinic is staffed with primary care, geriatric, pediatric, and obstetric- gynecologist physicians. Occasionally, specialists see patients in this location. The clinic accommodates private patients, patients that are a part of an HI insurance plan, and patients with Obra Social, a form of insurance for Argentine workers.

Female patients attending the out-patient clinic coming for routine appointments were approached in the waiting corridor by the primary investigator (PI) and asked to participate in the study. Involvement was voluntary and the PI screened prospective women for eligibility. To be eligible, a female needed to be 65 years of age or older and speak Spanish. Women with known dementia or who appeared confused and/or disoriented were considered ineligible. Staff at HI deemed that the protocol did not require International Review Board approval. Verbal consent was obtained from all participants.

A total of 328 women were screened, 75 were ineligible mainly because they did not meet the age condition. Of the 253 women who met the eligibility criteria, eleven refused to take part in the survey with time being the most frequent excuse and four did not finish the survey because they were called to go see their doctor.

Survey Administration

All participants underwent an in-person interview conducted in the waiting area of the clinic. All encounters were carried out by the PI. On average, the interview took ten minutes (range 7-15 minutes). The PI explained to each woman that "the purpose of the study is to find out what you know about urinary incontinence, or the involuntary loss of urine."

Instrument

The research instrument was forward translated into Spanish by a fluent, native speaker and validated by Spanish speaking employees at HI. A pilot test for comprehension was conducted on 40 female HI patients who met the eligibility criteria. The established resulting survey was administered to subjects and the following data were collected:

Demographics

Information about participants' age and level of education was obtained.

Knowledge and Familiarity To assess participants' knowledge about UI, a modified version of

the Incontinence Quiz (IQ), a tool established and validated by Branch and colleagues, was employed[8]. To the best of our knowledge, a validated Spanish language form of the IQ was not available. The IQ requires subjects to "agree", "disagree", or declare "I don't know" in response to a true or false statement about UI. For example: "Many over-the-counter medications can cause involuntary urine loss: agree, disagree, or I don't know"[5]. This format, when forward translated into Spanish, confused a pilot test group of female HI patients 65 years of age and older. It was determined that reframing the statement into a question would be a more familiar format for the women. The previous example was changed to: "Do you know if medications that you are able to buy over-the-counter can cause UI: yes they can cause UI, no they do not cause UI, or I don't know."

The resulting 12 question survey elicited data about participants' general familiarity with the topic of UI as well as their knowledge regarding the (a) causes of UI, (b) relationship of aging and UI, (c) doctor-patient communication about UI and (d) treatment options for UI. Subjects were also directly asked if they had UI. The type of UI - stress, urge, overflow, or mixed - was not differentiated in this study.

Prevalence

Women were asked the following question to assess if they had UI symptoms: "Have you ever lost urine during daily activities, at night, while coughing, sneezing, or laughing?" Answering "yes" to any of the above was considered a positive response. Participants who responded affirmatively were then asked: "Have you ever discussed your loss of urine with your primary care physician (PCP), gynecologist, a nurse or other healthcare professional?"

Statistical analysis

Data were analyzed using SNAP 10 professional. Surveys were coded to maintain anonymity. Demographic data were analyzed in order to characterize the study population. The frequencies of responses to each individual question were determined. Chi-squared tests were used to determine statistical associations between the independent and dependent variables. A P value of less than 0.05 was considered to be statistically significant.

The present study was approved by the Institutional Review Board and all participants provided written informed consent prior to performance the study interview to them.

RESULTS

A total of 238 women enrolled in the study. Table 1 describes the demographic characteristics of the sample. Mean age was 73.6 ± 5.8 years and median amount of education was 5 - 7 years.

Table 1. Characteristics (N = 238)

Variables	Mean	Median	SD	Range	No	%
Age (years)	73.6	73	5.8	65-88		
65-70					78	32.8
71-79					116	48.7
80≥					44	18.5
Education (years)		5-7		0-24		
0-4					41	17.2
5-7					97	40.8
8-11					40	16.8
12-14					32	13.4
15+					28	11.8

The participants' knowledge of and familiarity with UI are shown in Table 2. Almost all women, (97.5%) women were acquainted with the term UI. More than half of those surveyed could identify at least one women who had UI as well as spoke about the problem to their friends.

Table 2. Knowledge of and attitudes about UI (N = 238)

	Yes, N (%)	No, N (%)	I don't know, N (%)	Association with Education
Familiarity with the topic of UI				
Do you know what UI is?	232 (97.5)	6 (2.5)	N/A	
Do you know a woman that has UI?	129 (54.2)	109 (45.8)	N/A	
Do you talk with your female friends about UI?	124 (52.1)	114 (47.9)	N/A	
Causes of UI				
Do you think women develop UI more frequently than men?*	105 (44.1)	8 (3.4)	125 (52.5)	$P < .01$
Do you think over-the-counter medications can cause UI?*	50 (21.0)	5 (2.1)	183 (76.9)	
Relationship of aging and UI				
Do you think UI is a normal part of aging?**	152 (63.9)	35 (14.7)	51 (21.4)	$P < .01$
Doctor-patient communication about UI				
Has your doctor asked you about UI symptoms?	95 (39.9)	143 (60.1)	N/A	
Do you think older women with UI discuss their symptoms with a doctor?**	128 (52.5)	21 (8.8)	92 (38.7)	
Do you think it would be helpful for a woman with UI symptoms to tell her doctor?***	218 (91.6)	2 (0.8)	18 (7.6)	$P < .01$
Treatment options for UI				
Do you know about pads, diapers, or catheters to treat UI?	209 (87.8)	29 (12.2)	N/A	
Do you know about exercises that can help control UI?	75 (31.5)	163 (68.5)	N/A	$P < .05$
Do you know about an operation to treat UI?	75 (31.5)	163 (68.5)	N/A	

N/A = response was not an option * "Yes' is the correct answer ** "No" is the correct answer
*** "I don't have an opinion" replaced "I don't know" as an answer choice

A large number of women were uninformed about the causes of UI: 182 (76.8%) did not know that over-the-counter medications can cause symptoms. When asked about the frequency of UI in men and women, 125 (52.5%) did not know if women experience UI more frequently than men, 8 (3.4%) thought that men and women develop UI at equal rates, and 105 (44.1%) accurately knew that more women suffer from UI than men. The association between years of education and knowledge about the frequency of UI in women and men was statistically significant (P<.01): women with more education were more likely to know that women develop UI more than men.

Women were misinformed about the relationship between aging and UI. A large number of women, 152 (63.9%), incorrectly thought that UI is a normal part of the aging process. It is noteworthy that 78.6% of women with the highest level of education (15+ years) believed UI was a normal part of aging compared to 41.5% of women with the lowest level of education (0-4 years). The association between believing that UI is a normal part of the aging process and completed years of education was statistically significant (P<.01): the more years of education a woman had completed the more likely she was to think that UI is a normal part of aging.

A majority of women, 217 (91.6%), accurately believed that it would be helpful for a woman with UI to discuss this condition with a doctor. The association between level of education and beliefs about telling the doctor about UI was statistically significant (P<.01): women with more years of education were more likely to know that sharing UI symptoms with a physician would be helpful. There were 143 (60.3%) subjects who had not been asked by their PCP's about UI symptoms.

Within the sample, 87.8% knew of pads, adult diapers, and catheters to treat UI. However, 68.5% of women did not know about pelvic exercises or a surgical option to treat UI. The association between level of education and knowledge of pelvic exercises was statistically significant (P<.05): women with more education were more likely to know of these exercises.

Prevalence data varied depending on how the question was solicited. When asked to self-identify as having UI, 58 (24.4%) women acknowledged suffering from the condition. However, when the study population was specifically asked about UI

symptoms - such as urine loss during the day, night, while coughing, sneezing, or laughing - a larger group, 106 (44.5%), identified as having UI. Many participants, 46 (43.4%), who reported having UI symptoms did not consult a healthcare provider.

DISCUSSION

The purpose of this cross-sectional study was to determine what Argentine women 65 years of age and older know about UI and to establish the prevalence of UI in this population. Results for the 238 women studied showed that they were misinformed about the specific details (causes, aging, treatments, etc.) of UI. The information gleaned from this study elucidates the misconceptions that older Argentine women have about UI. Healthcare providers can use this information to develop interventions targeted towards increasing and correcting older Argentine women's knowledge about UI with the goal of improving management and treatment of symptoms.

Most women in this study believed that UI is a normal part of the aging process (63.9%), a finding consistent with other studies on the same topic. Kang found a similar result (61%) in a study of Korean-American women using the IQ [5]. Bush and colleagues, in a study of community-dwelling American minority and non-minority females, found that almost 50% believed UI to be a normal part of aging or childbirth[9]. Because of a series of physical, psychological, and functional changes that are associated with aging, the prevalence of UI increases with age; however, UI is not the result of normal aging[5]. Ouslander reported that UI in a geriatric population can be a "manifestation of a subacute or reversible process within or outside of the lower urinary tract."[10]. Educating older Argentine women about this fact, through either community educational programs or physician-initiated discussions, can correct their view that UI is an inevitable part of aging and will hopefully lead to more successful treatment of UI and the underlying process(es).

Interestingly, in the current study, 78.6% of the highest educated (15+ years) women believed that UI was a normal part of aging. This demonstrates that even educated women are frequently misinformed, consistent with results from previous studies[11]. Accurate UI information must be provided to all patients, regardless of their education status. Physicians should not assume that more highly educated women are better informed about UI because there is a clear gap between lay and medical knowledge[11].

Argentine women, as compared to women in other studies, are less knowledgeable about behavioral therapies that can be employed to treat UI. Among Korean-American women, 67% knew of exercises to help control UI compared with just 31.5% of Argentine women in the current study. Kang noted that Korean-American women were more knowledgeable about pelvic exercises compared to populations in other studies and attributed this finding to television programs and Korean language health magazines that educated Korean women about exercises they could do to decrease the effects of UI[5]. Hagglund and colleagues reported that women in their study might have been influenced to seek help for UI by reading magazine advertisements and/or watching television programs[4].

Using similar media, targeted to older Argentine woman, can help to increase their UI knowledge and correct their misconceptions. Public service announcements on Spanish TV and radio stations or advertisements in magazines should (a) tell women that UI is a real and common medical condition that is not a normal part of aging, (b) inform women that there are simple and effective treatments available and that their symptoms can worsen and lead to functional decline when left untreated, (c) provide information about causes such as over-the-counter medicines and possible underlying or reversible disorders, and (d) encourage females to seek treatment from a healthcare professional. Providing this same information on posters and brochures at senior centers as well as adult living facilities is another method to enlighten, educate, and empower women. This education, supplemented with information provided by healthcare workers, can help to increase UI knowledge and change women's attitudes about UI.

The prevalence data generated in this study varied based on the definition of UI used in the question. A higher prevalence, an almost two-fold increase to 44.5%, was found when women were asked to identify based on symptoms as compared to simply stating that they had UI. This finding is consistent with other research. Hagglund and colleagues reported that when wide definitions of UI were used, a larger number of women, including those with only minor symptoms, identified as having the condition[4]. Thus, PCP's when assessing for UI, should use broad questions to ensure capturing those experiencing only minor symptoms as well. Knowing that UI can be the manifestation of a variety of processes, it is important to identify women experiencing even minor UI symptoms to treat both the condition and a potentially harmful underlying cause.

Consistent with these findings, a larger group of younger women (those less than 73 years of age) identified as having UI when the question used a wider definition that included symptoms. It is likely that these "younger" women perceived UI as a neurological or senile disorder and did not initially self identify as suffering from this condition despite having obvious symptoms [11]. Because proper management depends on a woman's knowledge of UI, it is imperative that females are accurately educated about UI and its ability to affect women of all ages.

Although 91.6% of women surveyed believed it would be helpful to tell a doctor about one's UI symptoms, only 43.4% of those with UI symptoms actually sought out medical advice for this problem. This finding is consistent with previous research. Hsieh and colleagues found that among 1,514 Taiwanese women aged 60 years and older, 84.6% would tell a doctor if they had UI, but only 30.3% actually spoke to a physician[3]. Less than 20% of women in Finland and only 28.2% of European women sought out treatment as well[12].

Some study limitations merit consideration. First, women were interviewed in a crowded waiting area where complete privacy was not feasible. As a result, it is possible that the women were not being completely truthful in their responses. Second, the sample population was small which potentially limits the ability to generalize the results to all older Argentine females.

It is clear that educational programs, both at the community and healthcare-provider level, need to be implemented to increase UI knowledge in older Argentine females. A useful follow-up study would be one conducted in the same sample population of women that assesses UI knowledge after the sample group has been privy to educational materials. Healthcare workers that develop and implement UI educational programs designed to increase knowledge will lead likely see a rise in help-seeking behavior among older Argentine women with UI.

CONCLUSIONS

Argentine women 65 years of age and older are poorly informed about UI. Misconceptions and a lack of knowledge lead to the under-treatment of UI symptoms. Providing accurate information to women is imperative to ensure the proper treatment of this disorder.

Education about UI by individual physicians as well as at the community level can dramatically improve the quality of life for older Argentine women suffering from UI. Findings from this study provide important data specific to Argentine women. Healthcare providers and community workers that interact with this population can design targeted educational materials aimed to increase UI information based on what this study has established as the current level of knowledge.

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CONFLICT OF INTEREST

The authors of this paper declare that there are not conflicts of interests.

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Comment of the reviewer Dr. Alberto Enrique D'Ottavio. Professor and researcher. Facultad de Ciencias Médicas and Consejo de Investigaciones. Universidad Nacional de Rosario. Rosario, Argentina.

I consider acceptable work: "Urinary Incontinence: Knowledge, Attitudes, and Prevalence Among Females Argentine Older" since, in addition to interest and update refers to a location circumscribed conclusions Argentina. However, the findings can be compared with similar categories, eventually recorded in other localities in Argentina and abroad. In the latter regard, contributes its English version.

Comment of the reviewer Dra. María Cristina Tarrés, Professor and researcher. Facultad de Ciencias Médicas and Consejo de Investigaciones. Universidad Nacional de Rosario. Rosario. Argentina.

To my knowledge, this work, in addition to addressing facets of a topic of significant psychosocial impact, which affects the quality of life of patients as urinary incontinence in older Argentine women, revealed in its methodology, consistency and needed updating to be considered satisfactory for publication in the Electronic Journal of Biomedicine.

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RESISTENCIA A LOS ANTIBIÓTICOS EN CEPAS DE *KLEBSIELLA PNEUMONIAE*, *SERRATIA SPP.* Y *ACINETOBACTER SPP*. AISLADAS DE PACIENTES CON INFECCIÓN DEL TRACTO URINARIO - LIMA, PERU

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Comentario del revisor Dra. Maria Ángeles Mantecón Vallejo PhD. Sección de Microbiología. Hospital Universitario de Burgos. España.

RESUMEN:

Introducción: La infección del tracto urinario (ITU) es una de las infecciones más comunes en la práctica clínica. Bacterias gramnegativas como *Klebsiella pneumoniae, Serratia spp.* y *Acinetobacter spp.* pueden causar ITU.

Objetivo: Estudiar la resistencia antibiótica en cepas de K. pneumoniae, *Serratia spp.* y *Acinetobacter spp.* aisladas de ITU.

Material y métodos: Urocultivos fueron colectados de Enero 2003 a Diciembre 2003. La identificación de las bacterias aisladas incluyó características bioquímicas. La prueba de difusión con discos de Bauer-Kirby fue realizada.

Resultados: Un total de 106 cepas fueron evaluadas (41 de K. pneumoniae, 28 de *Serratia spp.* y 37 de *Acinetobacter spp.*). Entre los aislados de K. pneumoniae la resistencia a ampicilina (83%) fue notable. Los aislados de *Serratia spp.* exhibieron un alto nivel de resistencia a ácido nalidíxico (79%) y gentamicina (75%). En los aislados de *Acinetobacter spp.* altas proporciones de resistencia fueron observados frente a amikacina (81%), gentamicina(67%) y trimetoprima/sulfametoxasol (71%).

Conclusiones: En general, los patrones de resistencia a los antibióticos fueron altos. *Acinetobacter spp.* manifestó elevada prevalencia de resistencia (>50%) frente a los antibióticos incluidos.

PALABRAS CLAVE:*Klebsiella pneumoniae. Serratia spp. Acinetobacter spp.* Resistencia antibiótica. Infección del tracto urinario.

SUMMARY: ANTIBIOTIC RESISTANCE IN *KLEBSIELLA PNEUMONIAE*, *SERRATIA SPP.* AND *ACINETOBACTER SPP.* STRAINS ISOLATED FROM PATIENTS WITH URINARY TRACT INFECTION - LIMA, PERU

Introduction: Urinary tract infection (UTI) is one of the most common infections in clinical practice. Gram negative bacteria as *Klebsiella pneumoniae, Serratia spp.* and *Acinetobacter spp.* can cause UTI.

Objective: To study antibiotic resistance in K. pneumoniae, *Serratia spp.* and *Acinetobacter spp.* strains isolated from UTI

Material and methods: Urine cultures were collected from January 2003 to December 2003. Identification of isolated bacteria included biochemical characteristics. Bauer-Kirby disc diffusion test was performed.

Results: A total of 106 strains were evaluated (41 of K. pneumoniae, 28 of *Serratia spp.* and 37 of *Acinetobacter spp.*). Among K. pneumoniae isolates resistance to ampicillin (83%) was remarkable. The *Serratia spp.* isolates displayed a high level of resistance to nalidixic acid (79%) and gentamicin (75%). In *Acinetobacter spp.* isolates high resistance rates were observed against amikacin (81%), gentamicin (67%) and trimethoprim/sulfamethoxazole(71%).

Conclusions: In general, antibiotic resistance patterns were high. *Acinetobacter spp.* showed elevated resistance rates (>50%) against antibiotics included.

KEY WORDS: *Klebsiella pneumoniae*. *Serratia spp.*, *Acinetobacter spp.* Antibiotic resistance. Urinary tract infection.

INTRODUCCIÓN

La infección del tracto urinario (ITU) es un conjunto de procesos patológicos asociados a una respuesta inflamatoria como resultado de la presencia de microorganismos, generalmente bacterias. Después de las infecciones respiratorias, la ITU es la enfermedad más frecuente a nivel hospitalario y ambulatorio[1]; estimándose que el 48% de las mujeres sufrirá por lo menos un caso de ITU durante su vida[2].

Las bacterias gramnegativas son la causa más frecuente de ITU, siendo reportadas entre ellas Klebsiella pneumoniae, *Serratia spp.* y *Acinetobacter spp.*; las cuales también pueden ocasionar otras importantes infecciones hospitalarias[3-8].

Existe un problema actual respecto al tratamiento de la ITU ya que muchas cepas han desarrollado resistencia a diversos antibióticos. En Latinoamérica algunos estudios refieren el incremento de esta problemática[9-11].

Por lo expuesto, el objetivo de esta comunicación es evaluar la resistencia a los antibióticos en cepas de K. pneumoniae, *Serratia spp.* y *Acinetobacter spp.* aisladas en pacientes de sexo femenino con ITU atendidos en el Hospital Nacional Hipólito Unanue.

MATERIAL Y METODOS

Fue realizado un estudio retrospectivo en el Hospital Nacional Hipólito Unánue (nivel III), ubicado en el distrito de El Agustino, Lima, Perú. El hospital cuenta con 653 camas.

Los resultados de los urocultivos de los pacientes ambulatorios e internados de sexo femenino fueron registrados durante el periodo de 1º de Enero al 31 de Diciembre de 2003. Solo un aislado por cada paciente fue considerado.

Las muestras de orina fueron sembradas en agar Mc Conkey y agar CLED e incubadas a 37º por 18-24 horas. El aislamiento de las cepas fue realizado de acuerdo a la guía del Instituto Nacional de Salud12. No se tomó en cuenta la sintomatología ó la edad. La ITU fue establecida para un conteo 105 UFC/mL.

El análisis de susceptibilidad se realizó mediante la técnica de Bauer-Kirby de disco difusión13 con recomendaciones del NCCLS14. Las cepas con susceptibilidad intermedia se asumieron como sensibles. Los siguientes antibióticos fueron incluidos: ampicilina (10µg), amoxicilina/ácido clavulánico (20/10µg) ceftazidima (30µg), cefotaxima (30µg), ceftriaxona (30µg), imipenem (10µg), meropenem (10µg) aztreonam (30µg), ácido nalidíxico (30µg), norfloxacina (10µg), ciprofloxacina (5µg), gentamicina (10µg), amikacina (30µg), trimetoprima/sulfametoxasol (25µg), nitrofurantoína (300µg) y cefoperazona/sulbactam (75µg/30 µg). Como cepas control fueron utilizadas Pseudomonas aeruginosa ATCC 27853 y Escherichia coli ATCC 25922.

Para el análisis estadístico se utilizó la prueba Mid-P exacta para proporciones simples.

RESULTADOS

Durante el año de estudio fueron aisladas 41 cepas de K. pneumoniae (38,7% [IC 95%=29,4%-48,6%]), 28 de *Serratia spp.* (26,4% [IC 95%=18,3%-35,9%] y 37 de *Acinetobacter spp.* (34,9% [IC 95%=25,9%-44,8%]) sumando 106 cepas (10,6% [IC 95%=8,8%-12,6%]) de un total de 1002 microorganismos aislados en orina.

El análisis de la prevalencia de resistencia durante el periodo de análisis mostró que K. pneumoniae fue altamente resistente a ampicilina (83%), mientras que, la resistencia a amoxicilina/ácido clavulánico y nitrofurantoína fue moderada (13-16%). En el caso de *Serratia spp.* se registraron elevadas resistencias a ácido nalidíxico y gentamicina (75-79%), entretanto, frente a amikacina se constató una resistencia ligera (15%). Referente a los aislados de *Acinetobacter spp.* estos presentaron globalmente proporciones de resistencia por encima del 50%, siendo las más elevadas para trimetoprima/sulfametoxasol, gentamicina y amikacina (67-81%) (Tabla 1).

Tabla 1
Resistencia a los antibióticos en cepas de *K. pneumoniae*, *Serratia spp.* y *Acinetobacter spp.* aislados de pacientes de sexo femenino con ITU en el Hospital Nacional Hipólito Unánue, año 2003, Lima, Perú.

	K. pneumoniae	*Serratia spp.*	*Acinetobacter spp.*
	nº (%)	nº (%)	nº (%)
Ampicilina	34/41 (83)	†	†
Amoxicilina/ácidoclavulánico	5/39 (13)	†	†
Ceftazidima	10/38 (26)	†	13/21(62)
Cefotaxima	14/35 (40)	†	†
Ceftriaxona	†	10/21 (48)	†
Imipenem	†	†	10/19(53)
Meropenem	†	†	18/35 (51)
Aztreonam	12/24 (50)	†	†
Ácido nalidixico	10/24 (42)	15/19 (79)	†
Norfloxacina	12/29 (41)	1/2 (50)	7/14 (50)
Ciprofloxacina	†	†	18/29 (62)
Gentamicina	†	9/12 (75)	10/15 (67)
Amikacina	†	4/27 (15)	25/31 (81)
Trimetoprima/sulfametoxasol	†	7/19 (37)	20/28 (71)
Nitrofurantoína	5/31 (16)	9/16 (56)	†
Cefoperazona/sulbactam	†	1/5 (20)	†

† = No Probado

DISCUSIÓN

La ITU se encuentra entre las infecciones más comunes en la práctica clínica, resultando en una considerable ansiedad y morbilidad entre las mujeres[15]. La etiología y la frecuencia de los agentes causantes de ITU ha sido bien documentada[3, 16-18].

En nuestro estudio K. pneumoniae evidenció una alta resistencia a ampicilina (83%), lo cual corresponde con otros estudios realizados[19-20]. Esta elevada cifra indica que este antibiótico debe ser desestimado como opción terapéutica de primera línea.

En el caso de *Serratia spp.* la mayor resistencia se presentó frente al ácido nalidíxico (79%), similar a lo constatado en un análisis[21] aunque mayor a lo indicado en otro[22]. Este antibiótico es específico para la ITU aunque con la desventaja de que puede manifestarse una rápida aparición de bacterias resistentes.

Asimismo *Acinetobacter spp.* exhibió una considerable resistencia frente a amikacina(81%), cifra mayor a otros reportes[23-24]. Hallazgo poco menos que preocupante ya que este es un potente antibiótico indicado para infecciones severas.

Tanto *Serratia spp.* así como *Acinetobacter spp.* presentaron resistencia a trimetoprima/sulfametoxazol por encima del 20% que es el límite recomendado por The Infectious Diseases Society of America (IDSA)[25] y por lo tanto su uso no sería recomendable en el tratamiento empírico de la ITU.

Cabe resaltar que *Acinetobacter spp.* en general registró niveles de resistencia arriba del 50% para los antibióticos incluidos en el estudio. Hecho que no es sorprendente ya que la resistencia de *Acinetobacter spp.* a diversos antibióticos en años recientes se ha incrementado[8,26-29] debido probablemente a la relativa impermeabilidad de su membrana externa y a la exposición ambiental a un amplio grupo de genes de resistencia[30].

Lamentablemente no se dispuso de información de la producción de betalactamasas (AmpC, BLEE y carbapenemasas) las cuales tienen participación importante en el fenómeno de la resistencia a los antibióticos[31-32].

Algunas sugerencias para disminuir el impacto en la salud de la resistencia a los antibióticos son: evitar el uso indiscriminado de antibióticos por parte de los médicos, evitar la automedicación y el incumplimiento terapéutico luego de iniciada la mejoría clínica del cuadro, evitar la dispensación de antibióticos sin receta médica e incrementar las campañas informativas sobre uso racional de antibióticos[33].

Finalmente, los microorganismos estudiados registraron considerables niveles de resistencia a los antibióticos utilizados, especialmente *Acinetobacter spp.*, correspondería a las autoridades sanitarias tomar cartas en el asunto y viabilizar soluciones para evitar que se agudice este problema en ese hospital.

CONCLUSIONES

En general, los patrones de resistencia a los antibióticos fueron altos. *Acinetobacter spp.* manifestó elevada prevalencia de resistencia (>50%) frente a los antibióticos incluidos.

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La aportación que efectúan Luján Roca y col. presenta una serie que, aunque modesta y con cierta lejanía temporal es bienvenida, por la oportunidad que representa su difusión.

Con una estructura concisa presentan y discuten los hallazgos relativos al perfil de sensibilidad de los aislados de urocultivos de mujeres atendidas en Lima. Si bien integran muestras de procedencia comunitaria y nosocomial la validez de sus prevalencias en resistencia a tres microorganismos y diferentes antimicrobianos puede ayudar a definir la situación local. Los propios autores señalan medidas sanitarias a implementar de cara a mejorar la realidad que describen.

Sería deseable conocer la evolución temporal del tema y la descripción de los patrones moleculares de resistencia así como una aproximación deferencia da para conocer patrones de uso de antimicrobianos tanto en el medio ambulatorio como hospitalario.

Comentario del revisor Dra. Maria Ángeles Mantecón Vallejo PhD. Sección de Microbiología. Hospital Universitario de Burgos. España.

El trabajo presentado por Luján Roca y colaboradores pone de relevancia la importancia de conocer la microbiología y sensibilidad local con el fin de orientar el tratamiento empírico, en este caso de las infecciones urinarias.

El conocer las sensibilidades locales a los microorganismos más prevalentes, además de su evolución en el tiempo y los mecanismos que generan las resistencias, son algunas de las herramientas esenciales para llevar a cabo un adecuado uso de los antibióticos y evitar así la diseminación de resistencias sobre todo en el medio hospitalario.

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HYPONATREMIA SECONDARY TO A SODIUM DEFICIT IN PATIENTS ON CONTINUOUS OUT-PATIENT PERITONEAL DIALYSIS

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Version en español

INTRODUCTION

Hypotonic hyponatremia is an electrolytic disorder which can be caused by different mechanisms such as: an excess of body water and/or a deficit of sodium and/or potassium[1-2].

In patients on continuous out-patient peritoneal dialysis, hyponatremia can also be caused by some of these mechanisms and that, secondary to an excess of body water is the most frequent due to a failure in ultrafiltration[3].

In this report, we describe a clinical case of a patient who developed hyponatremia, while under continuous ambulatoy peritoneal dialysis, due to a deficit of sodium in the body secondary to a negative balance of sodium: body deficit of sodium.

CASE REPORT

58 year old patient with a history of:

- Arterial hypertension on a hyposodic diet (4 gr/day). Since the beginning of the dialysis treatment no antihypertensive drugs were required.
- Chronic kidney failure on peritoneal dialysis for one year with residual diuresis of 100 cc/day and a dialytic scheme of 4 volumen exchanges: 1700 cc, concentration: 1.5 % (x4) y 2.3% (x1), time of permanence: 6 hours, obtaining an ultrafiltration rate of 1200 cc/day. This was enough for an adequate doses of dialysis: weekly Kt/V: 2.00

In the routine monthly tests it was possible to observe asymptomatic hyponatremia (128 mmol/l), with normal glucemia, haemogram, proteinogram and lipidogram. At the time of the physical exam she had normal blood pressure, without pulmonary edemas or crackles. She was indicated hydric restriction of 800 cc/day and was instructed to return for a visual check-up in 48 hs. Nevertheless, in that check-up she was found to be thinner, more hypotense and not having recovered from her hyponatremia. She was not on any medication which could potentially induce hyponatremia (psychiatric, opioids and antiepileptic drugs).

Since the performed studies: encephalon, thorax and abdominal CT scans, and hormonal dosages (cortisol, thyroid hormone) showed normal values, then we decided to ask her to return to her normal hydration intake level (similar to the sum of urinary volume and peritoneal ultrafiltration), but also to start ingesting 6 gr/day of sodium. When after 48 hours she was re-assessed, the patient was already normotense and her natremia had increased to 138 mmol/l.

DISCUSSION

As it is clearly expressed by the Edelman ecuation:

$$\text{Natremia (mmol/l)} = \frac{\text{total body sodium + total body potassium}}{\text{Total body water}}$$

Hyponatremia can be induced by an increase in body water, as well as, a decrease in its content of sodium and/or potassium. It is already known that hyponatremia secondary to a disbalance of water/sodium, is caused by the alteration of the relationship of sodium/water which natremia represents.

In the case of hyponatremia secondary to a decrease in body potassium, it could be brought about as a consequence of adding sodium (cation) to the intra-cellular compartment, in compensation for the missing potassium (cation), to maintain electroneutrality of the intracellular medium. As a consequence of this, the concentration of sodium in the intravascular compartment would decrease and so would natremia [1-2]. Something similar would happen in states of malnutrition, where even in the case of normal kalemia, the intracellular deficit of potassium would induce hiponatremia due to this mechanism[3].

Hyponatremia in the patient on peritoneal dialytic treatment can be caused as a consequence of a disbalance in the sodium-water relationship in favor of the latter in relation with the quantity of water and salt ingested by the patient, as well as that excreted through urinary and peritoneal secretion (if it is preserved). It must be taken into account that during peritoneal dialysis sodium goes through the plasma to the peritoneal cavity due to the forces of diffusion and convection. However, as sodium is relatively sieved by the peritoneal membrane, the peritoneal fluid is usually hypotonic, which means it is richer in water than in salt, which in theory fosters the appearance of hypernatremia, especially in cases of short term permanence, as it happens in the case of the automatized case, if it weren`t for the release of vasopressin which stimulates thirst and the intake of fluids, thus normalizing the patient´s natremia.

Hyponatremia has been described in patients on peritoneal dialysis in the context of malnutrition, children fed with hyposodic formulas, hyperglucemia (dilucional hyponatremia) and using icodextrin. In the latter, osmotic retention of active metabollic derivatives in the intravascular would induce the passage of water from the intracellular and thus hyponatremia[4-7].

Hyponatremia is usually caused by an excess of body water; nevertheless when hyponatremia is secondary to a deficit of body sodium it has been described in very particular clinical situations such as: salt-losing interstitial nephritis, cerebral salt wasting syndrome and senile salt wasting syndrome[8-10]. In this report we describe a clinical case where the presence of hyponatremia is explained by a negative balance of sodium due to a low diet intake of this cation (hyposodic diet) and a relatively high and sustained egress of such (dialysed sodium), in the context of a hydric balance (ingested water – water excreted in urine and dialysis) neutral. It is for this reason, we observed that this hyponatremia did not improve when restricting the hydric intake, but increased sodium one.

CONCLUSION

In this report we have documented a case of hyponatremia secondary to a sodium deficit in a patient on continuous out-patient peritoneal dialysis.

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HIPONATREMIA SECUNDARIA A DEFICIT DE SODIO EN PACIENTE EN DIÁLISIS PERITONEAL CONTINUA AMBULATORIA

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English version

INTRODUCCIÓN

La hiponatremia hipotónica es un desorden electrolítico que puede obedecer a distintos mecanismos, tales como: un exceso de agua corporal y/o un déficit de sodio y/o de potasio corporales[1-2].

En los pacientes en diálisis periotneal continua ambulatoria la aparición de hiponatremia puede sucitarse también por alguno/s de estos mecanismos, siendo el más frecuente aquel secundario a un exceso de agua corporal producto de una falla de ultrafiltración[3].

En el presente reporte describimos un caso clínico de una paciente que desarrolló hiponatremia, estando en tratamiento de diálisis peritoneal continua ambulatoria, a raíz de un déficit corporal de sodio secundario a un balance negativo de sodio: déficit corporal de sodio.

CASO CLÍNICO

Paciente de 58 años con antecedentes de:

- **hipertensión arterial en tratamiento con dieta hiposódica (4 gr/día). Desde el inicio de la diálisis no había ya requerido medicación antihipertensiva.**
- **insuficiencia renal crónica en diálisis peritoneal desde hacía 1 año con diuresis residual de 100 cc/día y esquema dialítico de 4 cambios de volumen: 1700 cc, concentración: 1.5% (x4) y 2.3% (x1), tiempo de permanencia: 6 horas, logrando con ello una ultrafiltración de 1200 cc/día. Con esto alcanzaba una adecuada dosis de diálisis: Kt/V semanal: 2.0**

Se detectó en la rutina de control mensual una hiponatremia (128 mmol/l) que cursaba sin síntomas, glucemia, hemograma, proteinograma y lipidograma normales. Al examen físico se encontraba normohipotensa, sin edemas ni rales pulmonares. Se le indico restricción hídrica de 800 cc/día y se la citó a recontrol presencial en 48 horas. Sin embargo, en el control se la halló con menor peso, más hipotensa y sin haber resuelto su hiponatremia. No estaba hiporéxica ni estaba tomando ningún fármaco potencialmente inductor de hiponatremia (psicofármacos, opióides, antiepilépticos). Dado que, los estudios realizados: tomografías computadas de encéfalo, torax y abdominal, y los dosajes hormonales (cortisol, tiroideos) arrojaron valores de normalidad, decidimos entonces pedirle que retomase su ritmo de hidratación anterior (similar a la suma del volumen urinario y de ultrafiltración peritoneal), pero que además comenzase a ingerir 6 gr/día de sodio. Cuando a las 48 horas reevaluamos a la paciente estaba ya normotensa y su natremia se había elevado a 138 mmol/l.

DISCUSIÓN

Como claramente expresa la ecuación de Edelman:

$$\text{Natremia (mmol/l)} = \frac{\text{sodio corporal total + potasio corporal total}}{\text{agua corporal total}}$$

La hiponatremia puede ser inducida tanto por un aumento del agua corporal como por un descenso en su contenido de sodio y/o de potasio. Sabemos que en la hiponatremia secundaria a un disbalance del agua o del sodio, se generan a raíz de la alteración de la relación sodio/agua que precisamente la natremia representa. En el caso de la hiponatremia secundaria a una reducción del potasio corporal, ésta se generaría como consecuencia de ingresar sodio (catión) al compartimiento intra-celular, en compensación del potasio faltante (catión), a fin de mantener la electroneutralidad del medio intracelular. Como consecuencia de esto disminuiría la concentración de sodio intravascular y por ende la natremia[1-2]. Algo similar sucede en los estados de desnutrición, donde aun con kalemia normal, el déficit intracelular de potasio induciría hiponatremia[3].

La hiponatremia en el paciente en tratamiento dialítico peritoneal puede producirse como consecuencia de un disbalance en la relación sodio - agua a favor de esta última en función de la cantidad de agua y sal ingerida por el paciente y aquella excretada por vía urinaria (si la diuresis está respetada) y por vía peritoneal. Debe recordarse que durante la diálisis peritoneal el sodio pasa del plasma a la cavidad peritoneal merced a las fuerzas de difusión y convección. Pero como el sodio es relativamente tamizado por la membrana peritoneal, el fluido peritoneal suele ser hipotónico, es decir más rico en agua que en sal, lo cual en teoría propicia la hipernatremia, sobre todo en modalidades con permanencias de tiempo corto, como sucede con la modalidad automatizada.

Se ha descrito hiponatremia en pacientes en diálisis peritoneal en el contexto de desnutrición, niños alimentados con fórmulas hiposódicas, hiperglucemia (hiponatremia dilucional) y durante el uso de icodextrina. En este último caso, la retención de derivados metabólicos osmóticamente activos en el intravascular induciría pasaje de agua desde el intracelular y por consiguiente hiponatremia [4-7].

La hiponatremia hipotónica suele ser por lo general secundaria a un exceso corporal relativo de agua y/o a un déficit de sodio corporal ha sido descripta en situaciones clínicas muy particulares tales como la nefritis intersticial perdedora de sal, el síndrome de derrame cerebral de sal y el síndrome de derrame de sal senil [8-10]. En este reporte describimos un caso clínico donde la instalación de la hiponatremia se explica por un balance negativo de sodio debido a un escaso ingreso dietético de sodio (dieta hiposódica) y un egreso relativamente alto y sostenido de sodio (sodio dializado), en el contexto de un balance hídrico (agua ingerida – excretada por orina y diálisis) prácticamente neutro. De hecho, la hiponatremia que no mejoraba con restricción hídrica, si lo hizo con aumento en la ingesta de sodio.

CONCLUSIÓN

En el presente reporte hemos documentado un caso de hiponatremia secundaria a déficit de sodio en una paciente en diálisis peritoneal continua ambulatoria.

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PATOGÉNESIS DEL DENGUE HEMORRÁGICO (DH) SÍNDROME DE CHOQUE DEL DENGUE (SCD).

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RESUMEN:

En la patogénesis del dengue hemorrágico (DH) existen aún muchas interrogantes por contestar y la identificación de pacientes con alto riesgo de desarrollar esta patología sigue siendo un reto en la actualidad.

Existen varias hipótesis con respecto al desarrollo de este padecimiento, algunas enfocadas a las características moleculares del virus, y otras a las formas clínicas de la enfermedad así como los posibles mecanismos inmunológicos como la activación de la inmunidad innata, los anticuerpos naturales, el estado físico del virus, las reacciones mediadas por anticuerpos, el rol del sistema de complemento así como también la cascada de citocinas e incluso una base genética de la susceptibilidad al DH.

En este trabajo se abordan diferentes hipótesis para la dilucidación de la patogénesis del Dengue Hemorrágico

PALABRAS CLAVE:Dengue hemorrágico. Dengue severo. Patogénesis.

SUMMARY: There are still many questions to answer on the pathogenesis of hemorrhagic dengue (HD), and the identification of patients with a high risk of developing this disease still continues to be a challenge today.

There are several hypothesis as regards the development of HD, some focused on the molecular characteristics of the virus, and others on the clinical forms of the disease. Others include the possible immunological mechanisms, such as innate immunity, natural antibodies, the physical state of the virus, antibody-mediated reactions, the role of the complement system, as well as the cytokine storm, and even the genetic basis of susceptibility to HD.

This work will look at these different hypotheses in order to elucidate the pathogenesis of Hemorrhagic Dengue.

KEY WORDS: Dengue Hemorrhagic. Severe dengue. Pathogenesis.

INTRODUCCIÓN

A nivel mundial el dengue ha sido reconocido como una de las enfermedades emergentes más importantes en la actualidad. Aunque esta enfermedad normalmente causa una infección auto-limitada, algunos pacientes pueden desarrollar una enfermedad potencialmente mortal, el Dengue Hemorrágico (DH) /Síndrome de choque por dengue (SCD), la dilucidación del porque algunos pacientes pueden presentar este evento no está aún claro.

Se han propuesto varias hipótesis derivadas de estudios de investigación in vitro e in vivo con respecto a características moleculares del virus, las formas clínicas de la enfermedad así como los posibles mecanismos inmunológicos como la activación de la inmunidad innata, los anticuerpos naturales, el estado físico del virus, las reacciones mediadas por anticuerpos, el rol del sistema de complemento así como también la cascada de citocinas e incluso una base genética de la susceptibilidad al DH. En este artículo se mostrarán algunas de ellas que han tenido mayor peso en la investigación del DH/SCD.

2. Fiebre por dengue (FD), Dengue Hemorrágico (DH):

El dengue es una enfermedad que es producida por un arbovirus de la Familia Flaviviridae, transmitido al humano por la picadura de algunas especies de mosquitos infectados, de los géneros *Aedes* (o *Stegomyia*) como *A. aegypti, A. albopictus* principalmente y Ochlerotatus, actualmente se reconocen al menos 22 especies de vectores distribuidos en distintas regiones bio-geográficas[1]. Este virus tiene cuatro serotipos, DENV-1, DENV-2, DENV-3 y DENV-4[2].

Cada año, alrededor de 50 a 100 millones de personas en el mundo son infectadas con este virus; de éstas, entre 250 000 y 500 000 se convierten en casos de Dengue hemorrágico (DH) y 25 000 fallecen[2]. Del total de los casos infectados, 40 millones se diagnostican como clínicamente aparentes[3]; estos casos representan un espectro de enfermedades que van desde una enfermedad aguda llamada fiebre del dengue (FD) a la grave y potencialmente mortal que es el Dengue Hemorrágico/Síndrome de Choque del Dengue (DH/SCHD) o dengue severo[4, 5].

El DH o dengue severo, se caracteriza por la presencia de hemoconcentración debida a la fuga de plasma al espacio extravascular por aumento en la permeabilidad de los vasos sanguíneos, lo que determina la severidad del cuadro clínico y lo diferencia de la FD. Dicha hemoconcentración se manifiesta por hematocrito elevado y con frecuencia por la presencia de hemorragias (epistaxis, gingivorragia, sangrado urogenital, sangrado en sitios de punción, hemoptisis y sangrado del tubo digestivo) y la extravasación de líquidos (equimosis, hematomas o petequias).

El cuadro de DH, e incluso SCD, puede presentarse dos o tres días después de haber desaparecido los síntomas y aún la fiebre. Otros datos que suelen acompañar al DH son: dolor en área hepática, dolor abdominal, derrame pleural, ascitis, edema en diversos órganos, hepatomegalia o esplenomegalia, leucopenia inicial y leucocitosis posterior, hiponatremia, hipo-albuminemia, hipotensión con tendencia al acortamiento en el intervalo sistólico/diastólico.

Suelen presentarse además los siguientes datos: niveles elevados de aspartato sérico, aminotransferasas, nitrógeno y urea en sangre, albuminuria y, en algunos casos, reducción de los factores de coagulación y factores fibrinolíticos, tiempo prolongado de protrombina y parcial de tromboplastina; la radiología puede revelar un derrame pleural o líquido libre en cavidad abdominal. Durante el cuadro pueden presentarse complicaciones graves, como choque, insuficiencia hepática y renal; el daño hepático puede ser severo por lo que deberá monitorizarse el funcionamiento del hígado en forma sistémica; así mismo, se puede encontrar un cuadro de encefalopatía por hipoxia, edema cerebral, daño hepático, hemorragia intracraneal o alteraciones hidroelectrolíticas; también es frecuente un cuadro respiratorio no cardiógeno.

Por otra parte, la insuficiencia renal suele ser consecuencia de la hipovolemia especialmente en el SCD, por lo que deberá tenerse especial cuidado en el manejo de líquidos y evitar como complicación un edema pulmonar[6].

El Síndrome de choque (SCD) suele presentarse en el curso de un cuadro de DH, por lo general entre el tercero y quinto día de evolución; sin embargo, de acuerdo a la literatura, puede manifestarse inmediatamente dos o tres días después de un FD y excepcionalmente en pacientes asintomáticos o con cuadro febril inespecífico de dengue. Como en todo cuadro de choque, hay manifestaciones de insuficiencia circulatoria: piel fría y congestionada, cianosis peri-bucal o de las extremidades, vómito, llenado capilar lento taquicardia, tensión arterial disminuida o imperceptible, o bien reducción de la tensión diferencial (sistólica/diastólica) a menos de 20 mm/Hg, pulso rápido y débil o imperceptible, oliguria; puede haber además inquietud, agitación y alteraciones en el estado de conciencia como letargo o confusión. Se han identificado los siguientes signos de alarma que hacen inminente el cuadro de choque en un paciente de DH, permitiendo un manejo oportuno: dolor abdominal intenso y sostenido que pasa a ser uno de los componentes sintomáticos del cuadro al dato cardinal, vómito persistente, caída brusca de

que hacen inminente el cuadro de choque en un paciente de DH, permitiendo un manejo oportuno: dolor abdominal intenso y sostenido que pasa a ser uno de los componentes sintomáticos del cuadro al dato cardinal, vómito persistente, caída brusca de temperatura, de hipertermia a hipotermia, con frecuencia acompañada de sudoración, adinamia y lipotimias, inquietud o somnolencia[6].

2.1 fisiopatología:

La razón por la que el DH / SCD se produce en algunas personas no está claro. Los estudios realizados en las regiones endémicas sugieren que los anticuerpos preexistentes son un factor de riesgo para desarrollar de DH / SCD. La viremia y la trombocitopenia son las principales características de la infección por el virus del dengue.

En varios estudios realizados han encontrado una correlación significativa entre la cantidad de virus circulantes en los pacientes y el desarrollo de las formas graves de dengue. Un hallazgo crítico en los pacientes con dengue severo es la depresión transitoria de células hematológicas; sin embargo, las células responsables del aumento de la viremia del dengue están sin resolver a pesar de los intensos esfuerzos realizados.

El virus del dengue parece replicar y proliferar en muchas líneas celulares adaptadas, pero estas propiedades in vitro han sido extremadamente difíciles de ser reproducida en células primarias o in vivo[2,7]. Las características fisiopatologías que determinan la severidad de la enfermedad y que lo diferencia del FD son: perdida del plasma como resultado del aumento de la permeabilidad vascular y la hemostasia anormal, que ocurre en un grupo selecto de pacientes durante el curso de la infección por dengue[8].

El mecanismo subyacente que causa la DH/SCD es un tema de intenso debate entre investigadores. La evidencia actual sugiere que la respuesta inmune generada por el virus del dengue desempeña un papel clave en la cascada fisiopatológica de esta enfermedad[9]; también se ha asociado a niveles elevados de citosinas pro-inflamatorias en suero de pacientes infectados[10], así como otros mediadores producidos por las células fagocíticas y el mimetismo de anticuerpos[11].

Los pacientes que evolucionan a SCD fallecen a causa de la disfunción multi-orgánica y coagulación intra-vascular diseminada (CID). La duración del choque puede ser breve y acompañada de encefalopatía debido a trastornos metabólicos y electrolíticos[15].

3. Características del virus del dengue:

Es un virus ARN, monocatenario en sentido positivo, empaquetado dentro de una proteína y rodeado por un andamio icosaédrico y envuelto en una capa de lípidos[7]. Mide aproximadamente 50 nm de diámetro y el genoma viral alrededor de 11 Kb de longitud (una kilo-base, en genética, es equivalente a 1000 pares de bases de ADN)[12].

El genoma del virus codifica 3 proteínas estructurales y 7 no estructurales (ver figura 1)[2]. Las 7 no estructurales (NS1, NS2A, NS2B, NS3, NS4A, NS4B Y NS5) están involucradas en la patogénesis de la enfermedad severa. NS1 está implicada en la replicación del ARN viral y se expresa en la superficie de las células infectadas sin formar parte del virión[13]. Los niveles de NS1 secretada se correlacionan positivamente con los títulos virales[14]. Los niveles elevados de NS1 podrían implicar un papel importante en la formación de complejos inmunes en el DH[13].

Figura 1* . El genoma del virus del dengue.
Regiones no codificantes con estructuras terminales indicadas en líneas negras. Las proteínas estructurales son C, prM y E y las proteínas no estructurale son 1, 2A, 2B, 3, 4A, 4B y 5.

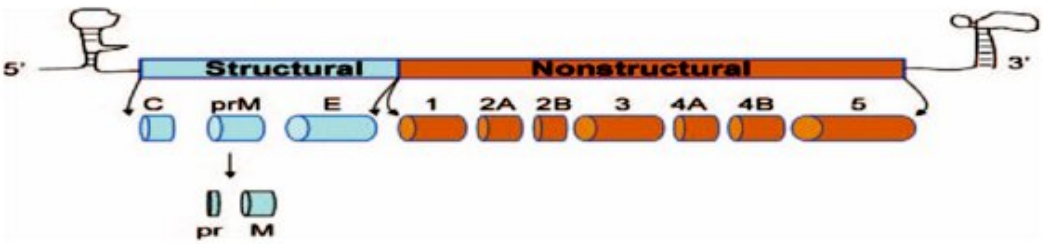

*Imagen tomada de: Noisakran S, Perng GC. Alternate hypothesis of the pathogenesis of dengue hemorrhagic Fever (DHF)/Dengue Shock Syndrome (DSS) in dengue virus infection. Experimental biology and medicine 2008. (233): 401-408.

La síntesis de la proteínas virales y ARN viral ocurren predominantemente en el citoplasma de las células hospederas. La replicación es lenta y comienza dentro de las 15 horas después de la infección[7]. Las proteínas de la envoltura, con la que el virus se une a receptores de las células anfitrión, lleva a cabo las funciones biológicas del virus, incluido el transporte del genoma viral en la célula huésped, la hemaglutinación de los eritrocitos, la inducción de anticuerpos neutralizantes, y las respuestas inmunes

protectoras[15].

4. Receptores del virus del dengue en células de mamífero:

Halstead et al[11], demostraron por primera vez que la infección el virus del dengue en leucocitos humanos de sangre periférica fue potenciada por la presencia de un anticuerpo no neutralizante. Esta reacción se vio mediada por receptores Fc gamma expresada en leucocitos. Estos resultados indican que la respuesta en la infección severa esta mediada por el receptor Fc en particular en la infección con un serotipo diferente al de la infección primaria[16].

Con respecto a la infección primaria y el contacto inicial del virus con las células hospederas, las investigaciones han estado dirigidas a la identificación de las moléculas receptoras en células de mamífero. La tabla 1 presenta un resumen de los receptores del virus en células en mamíferos, propuestos en varios estudios [17].

Tabla 1: Receptores de dengue virus (en células de mamíferos) propuestos es estudios previos*

RECEPTOR	PROPIEDADES	CELULA/ORGANO DONDE SE EXPRESA	SEROTIPO DEL VIRUS
HEPARAN SULTATE	Sultateglycosaminoglycan	Vero cells, BHK-21 cells SW-13 cells.	DENV1-4
NLc4Cer	Glycosphingolipid	Vero cells, ,BHK-21 cells K562 cells	DENV-1-4
DC-SING/L-SIGN	Dendritic cell-specifitlectin, CD29	Dendritic cells, Macrophage	DENV-1-4
Mannose receptor	Proteinwithlectinactivity	Macophage	DENV-1-4
HSP70/HSP90	Expression on plasma membrane heat-shock proteins	HepPG2 cells, SK-SY-5y cells, macrophage	DENV-2
GRP78	Expression on plasma membrane chaperon	HepPG2 cells	DENV-2
Laminin receptor	High-affinity laminin receptor MW: 37/67 KDa	PS clone D cells, HepPG2 cells	DENV1-3
CD 14-asociated protein	Protein associated with LPS receptor	Monocyte, macrophage	DENV-2
Unknownglycoprotein	CHO-dpd binding MW: 44/74 kDa	Vero cells	DENV-4
Unknowprotein	Trypsin-sensitive MW: 29 kDa	ECV 304 cells	DENV-2
Unknownprotein	Trypsin-sensitive MW: 65 kDa	NIE-115 cells SK-N-SH cells	DENV-2
Unknownprotein	Serotipe-specific binding MW: 78-182 kDa	HepPG2 cells	DENV-2-4

Mw: molecular Weight of interest protein . CHO-dpd binding: carbohydrate-dependent binding.
***Tomado y modificado de Hidari K, Suzuki Takashi. Dengue virus receptor. Tropical medicine and Health: 2011: 39 (4); 37-43.**

En los últimos 30 años se han realizado varios estudios para identificar y caracterizar los receptores que identifican el virus del dengue en las células hospederas. Varias moléculas se han propuesto como posibles receptores en células humanas y de mosquito[12]. En células de mamífero, los glicosaminoglicanos sulfatados (GAG's), lectinas que reconocen hidratos de carbono, glucoesfingolípidos (GSL), proteínas de unión a laminina, proteínas chaperonas y proteínas no definidas han sido reportadas como candidatos[17,18,19].

Otros estudios realizados por varios grupos de investigación sugieren que el Sulfato de Heparán y DC-SING (Células dentríticas específicas de la molécula de adhesión intercelular 3-acaparamiento no integrina) son indispensables para la infección por el virus en los seres humanos[20, 21]. Se piensa que el Sulfato de Heparán es un co-receptor que se asocia a otro grupo de moléculas para formar complejos funcionales y mejorar la eficacia de la infección del virus en las células hospederas[12]. El virus del dengue infecta a las células dendríticas a través de DC-SING específicamente expresados en este tipo de células. Otros estudios proponen que las moléculas de carbohidratos presentes en la matriz extracelular están fuertemente relacionadas con los receptores del virus del dengue[15].

El conocimiento de los mecanismos moleculares que subyacen en la interacción del virus del dengue con el receptor (s) en células humanas y/o de mosquitos es esencial para comprender la patología del dengue. Además, descubrir el mecanismo molecular(s) de entrada del virus es crucial para el desarrollo de nuevas terapias eficaces para el tratamiento de pacientes con esta patología. Investigaciones adicionales para dilucidar la naturaleza molecular del complejo DENV (1, 2, 3, 4) receptor son necesarias[4].

5. Hipótesis sobre la patogénesis de DH/SCD:

Existen varias hipótesis sobre la patogénesis del DH/SCD en individuos infectados con el virus del dengue. Estas son predominantemente derivadas de datos obtenidos en estudios realizados en regiones de países donde la enfermedad se produce de forma epidémica, y en experimentos in vitro[2]. Estas incluyen patogénesis dependiente de anticuerpos[22], patogénesis mediada por células T[2], fenómeno de tormenta de citoquinas[22], antecedentes genéticos[15], la diferencia entre tipos del virus[2], cantidad de virus en circulación durante la fase aguda[23] y el estado nutricional de los individuos infectados[22].

Algunas otras hipótesis sugieren varios factores estrechamente asociados a la infección por el virus del dengue y que no han sido dilucidados en su totalidad[2], entre estos se encuentran los factores relacionados con el calentamiento global, el estado físico del individuo infectado, transmisión vectorial, así como el sistema inmune innato, en el que está incluido el sistema del complemento, además del papel de las plaquetas en la patogenia de DH/SCD y la activación de células T[2,4,15,23].

Las interacciones entre el virus y el huésped que llevan a la inmunidad protectora frente a la patogénesis de la enfermedad, así como los mecanismos de la inmunidad anti-DENV, han sido poco estudiadas, enfocándose más al estudio del examen de la función del sistema inmune en el contexto de la patogénesis[2]. Comprender los mecanismos que regulan el equilibrio inmune entre la patología y la protección es fundamental para el desarrollo seguro y eficaz de tratamientos y vacunas contra el DENV[23].

5.1 Transmisión vectorial :

El dengue es transmitido por la picadura del mosquito portador de la partícula infecciosa (DENV). El vector puede servir como un anfitrión biológico (transmisión biológica) lo cual quiere decir que el virus requiere replicarse dentro del vector antes de ser transmitido a su nuevo hospedador (mamífero), o solo el virus requiere al vector como vehículo de transmisión (transmisión mecánica), es decir que el virus del dengue no requiere replicarse dentro del vector antes de que pueda ser transmitido a su nuevo objeto.

Si bien existen varios estudios sobre la transmisión biológica del DENV en el mosquito vector, hay poca información sobre la transmisión mecánica del DENV. En las zonas endémicas, especialmente durante las epidemias, la transmisión mecánica puede desempeñar un papel importante en la propagación del DENV, en ambos casos el vector parece inyectar directamente el virus en el vaso sanguíneo capilar[2].

La infección se inicia con la inyección del virus desde el mosquito vector a la corriente sanguínea del hospedero, pareciendo lógico que inicialmente en esta etapa el virus se encuentre con el sistema inmune innato del anfitrión (ver figura 2). Por lo tanto parece razonable llevar acabo estudios detallados sobre estos primeros eventos para poder identificar estrategias terapéuticas dirigidas a la prevención y desarrollo de DH/SCD en los periodos iníciales de la infección[2].

Figura 2* Encuentro del DENV con el sistema inmune innato en los vasos capilares. Hay varios componentes del sistema inmune distribuidos tanto en la circulación como en las barreras anatómicas (gran cantidad de células con actividad inmunológica)

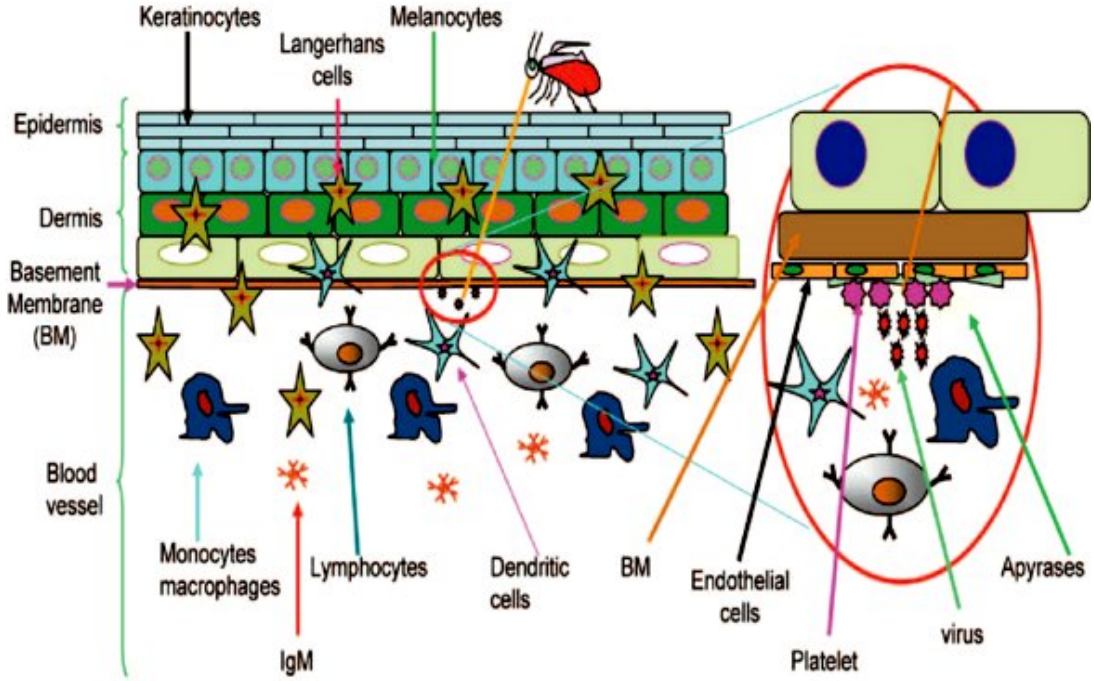

*Imagen tomada de Noisakran S, Perng GC. Alternate hypothesis of the pathogenesis of dengue hemorrhagic Fever (DHF)/Dengue Shock Syndrome (DSS) in dengue virus infection. Experimental biology and medicine 2008 (233): 401-408.

5.2 Estado físico del virus en individuos virémicos.

La viremia es la principal característica del DENV y única entre la familia flavivirus. La evidencia física de que si el virus se encuentra como una partícula libre, o está asociado a células y/o se encapsula en la membrana de la célula hospedera, es poco conocido[2].

La viremia puede estar causada por la presencia del virus en el plasma (partícula viral libre) o estar asociado a células, dentro de las plaquetas, linfocitos, monocitos, pero no probablemente en eritrocitos. En el caso de la viremia plasmática la cantidad del virus circulante es un factor crítico, los resultados de estudios sugieren que la mayoría de los virus circulantes en sangre están asociados a células[25]. De importancia es el hecho de que el virus asociado a células ayuda a propagar el virus en todo el cuerpo. Cabe destacar que también ha sido demostrado que el virus puede circular en forma de complejos inmunes, pero aun faltan estudios precisos sobre la cinética de cómo ocurre esto[2].

Ha sido complejo estudiar durante la viremia aguda a los pacientes humanos, puesto que tales pacientes se ven solamente envueltos en un cuadro febril. Es posible que después de la entrada del DENV en el torrente sanguíneo, el virus se introduzca a una célula permisiva donde se replica en cantidad suficiente para inducir la respuesta febril, después de lo cual pueden existir varias formas de evolución dependiendo del grado de viremia y de la respuesta del anfitrión frente a esta.

Realizar análisis minuciosos sobre estos primeros eventos durante el curso de la infección por DENV, tales como la cinética de la viremia asociados con cada etapa y la forma en la que existe el virus durante las mismas, pueden proporcionar una perspectiva en cuanto a las propiedades físicas de las partículas virales circulantes en sangre y conducir a la identificación de dianas únicas para una vacuna preventiva del desarrollo de la patogénesis de DH/SCD[2].

5.3 Sistema inmune innato:

El sistema inmune innato es la forma más antigua de defensa del huésped frente a la infección. Se ha documentado que este existe sin formas detectables del sistema inmune adaptativo en especies filogenéticamente más primitivas, lo que sugiere que ha tenido más tiempo evolutivo. Consta de varios componentes que en general van desde la piel hasta mecanismos efectores celulares y la codificación de moléculas por el genoma que actúan en sintonía para proteger al organismo de agentes extraños. Incluye anticuerpos naturales y factores implicados en el mantenimiento de la homeostasis[2, 26,27]. Sus características clave son la especificidad para reconocer el antígeno y que puede responder inmediatamente al contacto de este[25].

La respuesta de defensa inicial es eliminar o contener temporalmente a los agentes extraños y de este modo reducir o prevenir la infección. La respuesta a la infección por dengue virus en el periodo entre la infección y la aparición de signos clínicos es un evento que deberá de ser investigado con mayor profundidad.[27].

5.4 Anticuerpos naturales IgM:

La inmunidad humoral es principalmente mediada por células B, que producen diferentes clases de anticuerpos, tanto naturales como inducidos por patógenos. Los anticuerpos naturales IgM son producidos principalmente por CD5þ células B (células B1) y son un componente de la inmunidad innata[28]. Estos anticuerpos naturales circulantes no son específicos pero pueden unirse a patógenos, y así garantizar una protección temprana[26]. Los anticuerpos naturales pueden facilitar la captación de antígenos, el procesamiento, y presentación por parte de los linfocitos B a través del complemento y los receptores Fc[28].

Se ha sugerido que las células B son las principales células mono - nucleares circulantes en infectados por virus del dengue[30]. Interacciones entre la inmunidad innata y la respuesta inmune adaptativa son ahora ampliamente visto como esenciales para una respuesta inmune normal[30].

En los seres humanos el 30% de los anticuerpos en circulación son moléculas pentaméricas de IgM, también circulan una pequeña cantidad de hexamérica IgM, IgG e IgA naturales. Los anticuerpos IgM naturales están involucrados en el reconocimiento temprano de invasores externos y la eliminación de patógenos, como las bacterias y los virus[26,28]. La estructura multimérica de IgM es un fuerte activador del complemento; un pentámero de IgM enlazado puede desencadenar la vía clásica de activación del complemento, mientras que se requieren aproximadamente mil moléculas de IgG para realizar lo mismo[32]. Además, la IgM hexámero, a pesar de que circula en cantidades más pequeñas, es de 15 a 20 veces más eficiente en activar el complemento que la forma pentamérica de IgM[33].

Los complejos inmunes circulantes (CIC) en el suero de pacientes con DH / SCD fue reportada primero por Theofilopoulos et al en 1976[2]. El antígeno del dengue puede ser detectado en más del 50% de los CIC, y el aumento de los valores de plaquetas asociados a IgM se ha observado en casos de DH[2]. El complejo inmune de IgM ha sido encontrado consistentemente en las paredes de los vasos sanguíneos de papilas dérmicas o erupciones cutáneas de pacientes con dengue[34]. Sin embargo, el origen y la estructura de IgM en estos complejos inmunes no se han caracterizado[2].

El papel de los complejos inmunes de IgM circulantes en DH / SCD es poco conocido. Tal vez, los complejos inmunes que se adhieren a la superficie de las plaquetas pueden aumentar la destrucción de las mismas por el sistema retículo-endotelial en el hígado y el bazo, dando lugar a trombocitopenia durante la fase de choque en la enfermedad. Por lo tanto, los niveles de IgM, en particular de IgM naturales que tiene especificidad para el virus del dengue en un individuo pueden tener un impacto en el desarrollo de la infección y progresión del DH/SCD.

5.5 Las plaquetas:

Las plaquetas son un elemento esencial en la hemostasia. En estudios recientes han sido catalogadas como parte integral del sistema inmune innato y pueden ser efectores potentes de su respuesta[35]. Se ha demostrado que una molécula funcional CD154 (CD 40L) mejora la presentación de antígenos y aumenta la respuesta inmune adaptativa y se expresa en la superficie de las plaquetas[36]. Esto apoya el papel de las plaquetas en modulación de la respuesta inmune y la inflamación[37].

Los megacariocitos se producen en la medula ósea, y son los que dan origen a las plaquetas, estas son a-nucleadas rodeadas por membrana así como de citoplasma y gránulos de los mismos[35]. Circulan por los vasos sanguíneos y funcionan para controlar la integridad del sistema vascular. Hay dos formas de plaquetas circulantes, unas de reposo como discos y una forma activa como filopodios.

Estructuralmente, la configuración del cito-esqueleto en estas formas es diferente ya que tienen diferentes conjuntos de actina y micro-túbulos[36]. Cuando el revestimiento de un vaso sanguíneo está traumatizado, las plaquetas son estimuladas a través de diversos mediadores para ir al sitio de la lesión, donde forman un tapón para reducir la pérdida de sangre.

Todas las respuestas funcionales de las plaquetas deben estar estrictamente reguladas para asegurar la formación del coágulo, que debe ser del tamaño suficiente para sellar el área dañada, sin interrumpir u ocluir el flujo de sangre a los órganos vitales[37]. Por lo tanto, el deterioro de su función puede aumentar el riesgo de fragilidad vascular dando lugar a una hemorragia. Esto puede ser un mecanismo importante de pérdida de plasma en formas graves de dengue[2].

Una de las principales manifestaciones clínicas de la enfermedad del dengue es la trombocitopenia[2]. Esto surge debido a la disminución en producción y aumento en la destrucción de las plaquetas[36]. El grado de trombocitopenia así como la activación del complemento no parecen estar correlacionada con la gravedad clínica de DH[2,4].

Durante la infección por el virus del dengue, las plaquetas pueden proporcionar un escudo maravilloso para el virus frente a la neutralización de anticuerpos preexistentes. Hay algunos estudios que sugieren que el virus de dengue puede asociarse con plaquetas, directa o indirectamente, a través de anticuerpos[2]. Asumiendo que este es el caso, se puede suponer que los complejos virus-anticuerpo-plaquetas pueden aumentar la fagocitosis o ser devorados por los macrófagos o monocitos a través del receptor de Fc como se ha sugerido por otros autores[34].

Últimamente se demostró que el DENV utiliza una polimerasa con transcripción inversa y se ha hallado purificado en plaquetas de pacientes infectados con el virus[2]. El punto interesante de estos hallazgos es que la trombocitopenia que se ve en pacientes con

DH / SCD no sólo se produce por la destrucción de las plaquetas sino también por el virus (citotoxicidad directa), pero además puede ser causada por la destrucción de las plaquetas después de la unión de anticuerpos específicos del DENV contra las plaquetas infectadas con virus (inmuno-toxicidad mediada por anticuerpos)[38]. También es posible que las plaquetas puedan servir como un reservorio para la replicación del virus del dengue[2].

5.6 Sistema del complemento

El estudio realizado por Avirutnan et al[39] ha arrojado datos sobre el doble papel del sistema del complemento en la protección y en la patogénesis de la infección por DENV.

El sistema del complemento, está integrado por más de 30 diferentes proteínas de superficie celular y otras solubles, es un componente importante de la respuesta inmune innata contra diferentes patógenos que se activa a través de las vías clásicas, lectina y alternativa, mismas que controlan las infecciones virales a través de múltiples mecanismos, incluyendo la lisis de los viriones o células infectadas.

La vía clásica se activa por la unión de C1q a los complejos antígeno-anticuerpo; la vía de la lectina implica el reconocimiento de carbohidratos de las estructuras de patógenos a través de lectina fijadora de manosa (MBL) y la vía alternativa que se activa a niveles bajos a través de la hidrólisis espontánea de C3[4].

La mayoría de los estudios que examinan las interacciones entre DENV y sistema de complemento se han centrado en el papel que juega el complemento en la patogénesis de SCD[4].

Avirutnan et al[40] en un estudio prospectivo realizado propuso que la proteína no estructural 1 (NS1) del DENV podría activar el complemento, y por otro lado, altos niveles de NS1 y varias proteínas del complemento se ha encontrado que están correlacionados con la gravedad de la enfermedad[41].

Shresta en otro estudio prospectivo demostró que los niveles de los factores del complemento D y H (es decir, proteínas reguladoras de la vía alternativa) y la proteína MBL se encontraron más elevados en pacientes con DH que en los de FD (fiebre del dengue)[4]. Estos estudios postulan una relación entre la actividad de NS1 y la activación del complemento o una alteración en la regulación de la activación del complemento en la patogenia del dengue, dando un papel importante al sistema del complemento en el contexto de la inmunidad protectora.

En estudios in vitro han demostrado que ADE (aumento de la infección dependiente de anticuerpos) reduce las proteínas del complemento en la infección por DENV lo que sugiere que el complemento puede jugar un papel en la limitación de la enfermedad mediada por ADE[4].

Recientemente, los estudios in vitro con NS1 de DENV han señalado que la proteína viral se une a C4 y C1s[40] o C4BP para antagonizar la activación del complemento, lo que implica que NS1 es una molécula de evasión del sistema inmune in vivo[43]. Otros estudios muestran cómo DENV pueden emplear mecanismos múltiples para revertir la activación del complemento y sugieren que el sistema del complemento es un importante factor en la defensa del huésped contra DENV[42].

En otro estudio realizado por el grupo de Avirutnan et al.[39] examinó el papel del sistema del complemento en la protección contra la infección de DENV, y los resultados obtenidos indican que este sistema tiene un papel importante en el control de la infección por DENV y en la gravedad del dengue en humanos[4]. Este mismo grupo de investigadores han realizado experimentos usando sueros de ratón para determinar qué vías del complemento contribuyen a la neutralización de DENV in vitro[39].

Experimentos con modelos en ratón con pérdida de función de varias proteínas del complemento demostraron que la vía MBL era crítica para la neutralización del serotipo DENV-2,[4,39]. Basándose en estos resultados, los autores realizaron experimentos adicionales purificando y utilizando MBL humano y demostraron que esta podría directamente neutralizar DENV-2 y dicha neutralización fue más eficiente a temperaturas más altas (37° C y 40° C) que a temperatura ambiente[4].

En conjunto, estos resultados y observaciones sugieren que la vía MBL contribuye a la protección contra la infección por DENV en los seres humanos. Las deficiencias en la MBL son relativamente comunes en los seres humanos. La deficiencia de MBL ha sido asociada con una mayor susceptibilidad a muchas enfermedades infecciosas, incluyendo las infecciones virales[4,44].

5.7 Aumento de infección dependiente de anticuerpo. ADE:

Durante las infecciones secundarias con un serotipo del virus del dengue (heterotipo) existe una fuerte evidencia en estudios in vitro como in vivo que sugieren que los niveles pre-existentes, no-neutralizantes, y no protectores de anticuerpos contra dengue aumentan la replicación del virus en células con receptor Fc, especialmente monocitos y macrófagos[21].

Estudios sero-epidemiológicos llevados a cabo durante las epidemias de DH en Cuba en 1981, 1997 y 2001-2002[23] y en otras zonas endémicas confirmó que la infección por dengue secundario fue un factor de riesgo significativo en más de 97% de los casos graves[21] y después de la infección primaria, especialmente por DEV-2 y DEV-3 y después de una primera por DENV-1. Sin embargo, todos los serotipos de dengue se ha demostrado que son capaces de causar DH/SCD en contraste con la enfermedad más leve que se asocia a cargas menores virales y altos niveles de anticuerpos neutralizantes preexistentes en infección

secundaria heterotípica.

Además el ADE, realiza reacción cruzada contra la proteína NS1 relacionada con el daño a células endoteliales al inducirlas a apoptosis. Los estudios in vitro indican que la producción de citoquinas y quimioquinas en células endoteliales, incluida la interleucina-6 (IL-6), IL-8 y MCP-1(Proteína quimiotáctica de monocitos 1), se encuentran aumentadas después del tratamiento con anticuerpos anti-NS1 que sugiere la posibilidad de una enfermedad auto-inmunitaria en la patogénesis de DH/SCD basado en el "mimetismo molecular"[23].

También, anticuerpos en la reactividad cruzada con el plasminógeno (debido a una similitud a la glicoproteína de la envoltura del DENV y una familia de factores de coagulación) podrían desempeñar un papel en la etiología de la hemorragia en el DH/SCD[23]. Se ha observado la persistencia de anticuerpos NS1 por mucho tiempo después de que la infección por dengue se ha resuelto. Por lo tanto, esto puede ser importante para entender cómo tales mecanismos autoinmunes están limitados cuando la infección se está produciendo.

Más reciente, en resultados preliminares, una investigación propuso el posible papel de la citotoxicidad celular dependiente de anticuerpos ADCC[45], esta actividad se detectó en sueros de pacientes con DH, pero no de los pacientes con la fiebre del dengue, por lo tanto se sugiere un posible papel de ADCC en la patogénesis de DH / SCHD. Se requiere investigación adicional para comprender plenamente el significado completo y el papel de ADCC en la patogenia de DH / SCD y su importancia en la activación de células T[23].

5.8 Activación de células T:

Hay una fuerte evidencia de la activación de células T in vivo durante la infección por DENV y tal activación de las células T CD4+ y CD8+ es mayor en los pacientes con DH que en los que tienen FD[45]. Después de la ADE (aumento de la infección dependiente de anticuerpos) y de la replicación viral en monocitos y macrófagos se presentan antígenos virales en conjunto con moléculas antígeno de linfocitos humanos en la superficie de dichas célula.

A continuación se produce la activación de células CD4+, Células CD8+ y Células T de memoria que fueron sensibilizadas durante una infección previa lo que conduce a la proliferación y liberación de citoquinas pro-inflamatorias tales como interferón gamma (IFNg) y factor de necrosis tumoral alfa (TNFa)[46,47]. Estas citoquinas pueden actuar directamente sobre las células endoteliales vasculares que resulta finalmente en la fuga del plasma[23].

Estudios en niños con DH/SCD evidenciaron la asociación de la enfermedad con altos niveles de activación de células T acompañadas de una masiva apoptosis[21]. Un estudio realizado en niños tailandeses infectados por DENV concluyó que las células T muestran una baja afinidad por el virus infectante (virus de infección previa) y una mayor afinidad por otro serotipo, la reacción cruzada presente en el dengue específicamente generada por las células T ha demostrado que induce a la exacerbación de la producción de citoquinas y con ello al aumento de la permeabilidad vascular induciendo a DH/SCD[23,48].

5.9 Cascada/tormenta de citoquina:

Actualmente se cree que después de la activación masiva de linfocitos T de memoria, una cascada de citoquinas actúa sobre las células endoteliales vasculares, lo cual sería el evento crítico que conduce a la fuga de líquidos y proteínas. Las concentraciones de citoquinas por las células T, monocitos, macrófagos y células endoteliales se ha demostrado que se encuentran incrementadas en suero de pacientes con DH/SCD y en especial TNFa, IL-2, IL-6, IL-1, IL-8b e IFNg. Estos hallazgos tienen el respaldo de estudios en los que se analizaron sueros de pacientes con DH/SCD originarios de Vietnam, India y Cuba, quienes mostraron niveles altos de IFNg y TNFa e IL-10.

También existen evidencias científicas que demuestran que las citoquinas pueden inducir a la liberación y producción de otras citoquinas, esta compleja red interactiva provoca inducción de nuevas elevaciones en los niveles de citoquinas y otros mediadores químicos[23]. Las citoquinas también tienen a menudo efectos sinérgicos, por ejemplo, TNFa, IL IFNg 1-ADE y juntas pueden inducir un aumento mayor en la permeabilidad, en comparación a cuando cada una de estas citoquinas actúa de forma individual. Además, IFNg también es capaz de incrementar la expresión de los receptores de FCG en monocitos y macrófagos facilitando así la replicación viral[23].

La respuesta de las citoquinas está estrechamente ligada a la activación de células T y es aceptado que l ADE-VIRAL active una secuencia de liberación de citoquinas que estrictamente no es un proceso lineal, sino más bien una compleja interacción de acontecimientos patológicos que en última instancia desencadenan la aparición de DH/SCD, caracterizado por aumento de la permeabilidad vascular e insuficiencia circulatoria.

La probabilidad de que las citoquinas, en lugar de los virus sean responsables del daño a las células endoteliales durante DH fue sugerido por un estudio inmuno-patológico en tejidos humanos de pacientes con DH donde la presencia de antígenos de dengue en las células endoteliales se pensaba que era debido a la deposición de complejos virus-anticuerpo en lugar de la replicación viral que se produce en monocitos y macrófagos[40].

5.10 Base genética de DH/SSD:

La diversidad de las manifestaciones clínicas de las infecciones de dengue plantea la posibilidad de una base genética para la regulación de la expresión de esta enfermedad. La resistencia al DH observado en los cubanos de ascendencia africana y mayor riesgo en negroides de ascendencia caucásica apoyan la hipótesis genética[15].

Se ha demostrado que algunas enfermedades están asociadas con los alelos del antígeno leucocitario humano (HLA), el receptor de la vitamina D y Fc?IIa el polimorfismo del locide HLA de clase1 loci el cual fue encontrado asociado con una mayor susceptibilidad a DH en Vietnam[49]. Esta asociación fue confinada a la región HLA-A y no del gen HLA-B. Los niños con HLA-A * 24 fueron más susceptibles para DH en comparación con los niños con HLA-A * 33 Además, HLA-A * 0203 se encontró que se asocia con infecciones por dengue menos graves, independientemente del serotipo del virus infectante en las infecciones secundarias.

El polimorfismo en cinco genes HLA es decir, IL-4, IL-1RA, MBL, VDR, y FccRII se encontró que pueden aumentar la susceptibilidad a DH. Una mutación funcional en la región promotora de DC-SIGN se asoció con la susceptibilidad a dengue leve, pero no a DH[50]. La acción inmuno-reguladora del receptor de la vitamina D incluye la activación de monocitos, la estimulación de respuestas inmunes celulares, y la supresión de la producción de inmunoglobulina y proliferación de linfocitos[15].

6. CONCLUSIÓN:

Las hipótesis planteadas en este artículo derivadas de estudios in vivo e in vitro, proponen varios mecanismos para dilucidar la patogénesis del DH/SCD, varios de ellos no necesariamente excluyentes como se sugiere con la presencia de los niveles pre-existentes, no-neutralizantes, y no protectores de anticuerpos, con reactividad cruzada contra la proteína NSI del virus del dengue, los cuales podrían estar asociados al aumentado de la replicación del DENV en células con receptor Fc, especialmente monocitos y macrófagos y, relacionados con el daño a células endoteliales al inducirlas a apoptosis.

El otro mecanismo relacionado implica a los linfocitos CD8 específicos contra el virus del dengue los cuales se someten a apoptosis debido al agotamiento que sufren al enfrentar a las células infectadas por este virus. Ambos mecanismos llevan a una pérdida inmunológica la cual se le ha relacionado como un disparador importante en la activación del complemento. Otro mecanismo plantea que después de la activación masiva de linfocitos T de memoria, una cascada de citoquinas actúa sobre las células endoteliales vasculares, lo cual sería el evento crítico que conduce a la fuga de líquidos.

La hipótesis que plantea una base genética se sustenta en los estudios de investigación que han evidenciado cierta resistencia al DH/SCD en determinados grupos raciales.

No se descarta que muchos de estos mecanismos propuestos puedan interaccionar y llevar al desarrollo del DH/SCD. Dilucidar la patogénesis del DH/SCD puede permitir en un futuro el establecimiento de marcadores predictivos que permitan detectar los pacientes de alto riesgo antes de desarrollar los signos y síntomas en esta enfermedad que ha causado muchas muertes a nivel mundial.

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Comentario del revisor Prof. Dr. José María Eirós Bouza MD. PhD. Catedrático de Microbiología. Facultad de Medicina de la Universidad de Valladolid. España.

El grupo de Pérez Contreras realiza una aportación esclarecedora sobre la pato génesis del Dengue hemorrágico. Si bien en nuestra Europa la carga de enfermedad que genera es mínima, en el mundo su protagonismo no debe ser minusvalorado.

Los autores revisan diferentes aspectos que se asocian a su desenlace y esclarecen determina dos interrogantes. Adolece su contribución de datos originales pero no por ello decae su interés para el estudioso de los mecanismos básicos de esta patología

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Comentario del revisor Dr. Santiago González Quijada MD. PhD. Sección de Medicina Interna. Hospital Universitario de Burgos. España.

Las contribuciones sobre la Infección por Dengue son siempre bienvenidas por la incidencia y la capacidad letal que presenta esta enfermedad a nivel mundial.

La revisión del grupo de los investigadores de la Universidad Autónoma de Puebla constituye una aportación interesante desde el punto de vista patogénico del Dengue Hemorrágico. Realizan un interesante análisis de las hipótesis vigentes sobre la patogénesis de la enfermedad, y además son capaces de interrelacionarlas y sacar conclusiones que podrían redirigir ciertas lineas de investigación. Dilucidar la patogénesis del Dengue Hemorrágico es importante, ya que podría permitir el establecimiento de los factores de riesgo relacionados con la severidad del proceso.

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Letter:

On age dependence of peripheral augmentation index.

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Sir:

The possibility to continuously assess changes in blood pressure dictates the need to find proper ways of obtaining clinically relevant information from such signals. In the simplest linear case scenario pressure changes are directly proportional to volume changes. This could give some theoretical soundness to the use of photoplethysmographic signals for similar purposes[1]. Even when the PPG signal is not a "purely volumetric" signal, the fact that it is at least partially related to volume, can justify , in the sense of the Takens theorem, its use as a surrogate of continuous pressure signal. If this will work in practice, the amount of resources saved and the number of patients potentially evaluated can increase substantially.

Augmentation Index (AIx) has been widely used as a purported indicator of arterial stiffness. AIx is defined as the proportion of the second, reflected wave to the systolic wave. In particular it has been shown that peripheral AI (pAIx) reliably reflects the relationship between central and peripheral pulse pressure[2]. Plausibly, AIx seems to measure the contribution of an early and substantial reflected wave superposed to an incident wave. It seems also reasonable to expect that the AIx will increase with both higher amplitude of the reflected wave as well as with a higher pulse wave velocity.

On the other hand, it is known that both the amplitude and velocity of the reflected wave tend to increase with age and this would lead to steady increases in AIx with age[3]. Indeed, a positive age correlation has been confirmed in some reports[4]. Unexpectedly, there are various reports claiming that AI is not always significantly correlated with age. Some attempts to explain this fact have been put forward based on both mathematical[5] and physiological grounds[6].

Here, age dependence of pAIx assessed from Photoplethysmographic signals recorded from a sample of purportedly healthy subjects (10-87 y) is addressed. Also, a simulation study was carried out to clarify the possible relationship between peripheral pAIx and both amplitude- and velocity of the reflected wave.

Subjects. Fifty three volunteers were recruited in the city of Orense. They were free of clinical cardiovascular disease and medication, and Body Mass Index never surpassed 31 kgxm-2. Approval was obtained from the local research ethics committee, and written informed consent was obtained from all participants. Five-min-duration photoplethysmographic signals were obtained from the pointer finger of the right arm with the subject in supine position, using a validated oximeter (Nellcor 395, USA). Signals were digitized at 100 Hz and saved as ASCII files. Continuous pulse pressure signals digitized at 125 were downloaded from the "Fantasia" data base available at www.physionet.org.

Data analysis. Peripheral AIx determination. AI was estimated over an average wave obtained automatically from the superposition of at least 65 individual waves. For wave averaging, a pattern vector of length L (usually about 90 data points) was picked by visual inspection. Correlations were measured between the pattern vector and each individual vector of length L starting at the point I of the original signal. The obtained vector of correlations (corresponding to about 100 seconds of recording) was then submitted to further analysis. Those vectors with from the signal having a correlation higher than a certain threshold "Th" and corresponding to a local maximum of correlation were picked as individual waves and entered as rows of the matrix M of the waveforms. From M the average waveform was obtained from averaging over all rows. The main virtue of the method is that a representative wave is obtained without the need to rely on subjective opinions of experts. After estimating the first and second derivatives of the average wave, the inflexion points were determined. Peripheral AIx was obtained as the ratio of the amplitude at the inflexion point to the right of the peak to the maximum amplitude[2].

Simulations. The systolic part of the PPG wave was represented as the composition of an incident and a reflected wave. Expecting minor loss of generalization, each individual wave was simulated with a bell shaped symmetrical and infinitely derivable curve of the type:

$$y_1(t) = e^{\left(\frac{t-t_1}{\sigma}\right)^2}$$

$$y_2(t) = ae^{\left(\frac{t-t_2}{\sigma}\right)^2}$$

$$y(t) = y_1(t) + y_2(t)$$

The relative amplitude of the reflected wave (a) changed from zero to 1; the value of t1 was fixed in our simulations at 40 (corresponding to 400 ms). For t2, values ranged between 46 and 65 (roughly corresponding to velocities between 4 and 17 m/s for a sampling rate of 100 Hz and a distance of 1 m between abdominal aortic bifurcation and the pointer finger). Aix was determined from these simulated signals using the same algorithm as the one used for average waves.

Statistical analysis. Linear and nonlinear regression was indicated in some scatter plots, whereas other data are presented as means and standard deviations.

Correlation of p AIX with age. Our data exhibited a negative correlation between pAIx and age (r=-0.505; p=0.0039; Figure 1). Since the PPG signal is a mere surrogate of pulse pressure, this result can be a consequence of the poor quality of the PPG signal as a proxy for pulse pressure signals.

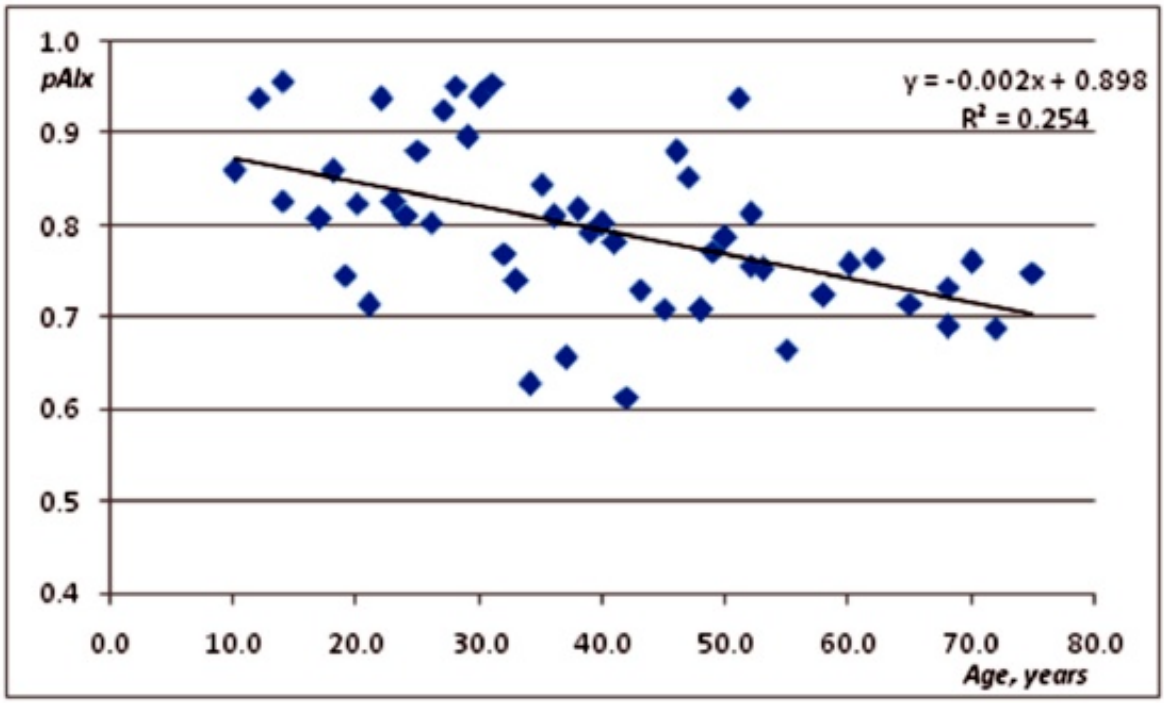

Figure 1. Scatter plot relating peripheral augmentation index as a function of age.

Thus we decided to explore if pAIx changes with age in a sample of clinically healthy young and elderly patients recorded with a continuous pulse pressure technique. Data were downloaded from the "Fantasia" database at physionet.org.

Results did not support the hypothesis of higher pAIx values among elderly patients. Here pAIx was estimated at 0.80 ± 0.16 among young subjects and 0.82 ± 0.11 among elderly (n. s. nonparametric permutation test)

After confirming that pAIx does not necessarily increases as age increases, the next step was to explore if a model wave composed of an incident and a superposed reflected wave will behave as intuitively expected.

For a comprehensive answer to this question, different waveforms shapes and a large set of possible parameters configurations need to be explored. In this case we explored the simple case of two symmetrical and infinitely derivable waves represented by a Gaussian-like function. (See methods section). We tried to make the wave duration comparable to that in real recordings (about 100 data points corresponding to 1000 ms with a 100 Hz sampling rate).

Fixing the velocity at 5 m/s (corresponding to a 200 ms time shift for a standard distance of 1 meter between aorta bifurcation and pointer finger) and changing the reflected wave amplitude, it was obtained that the simulated AIx steadily increases with amplitude (figure..) In this case the results from numerical experiments are coincident with the apparent expectations. Similar results are obtained if velocity is fixed at 20 m/s.

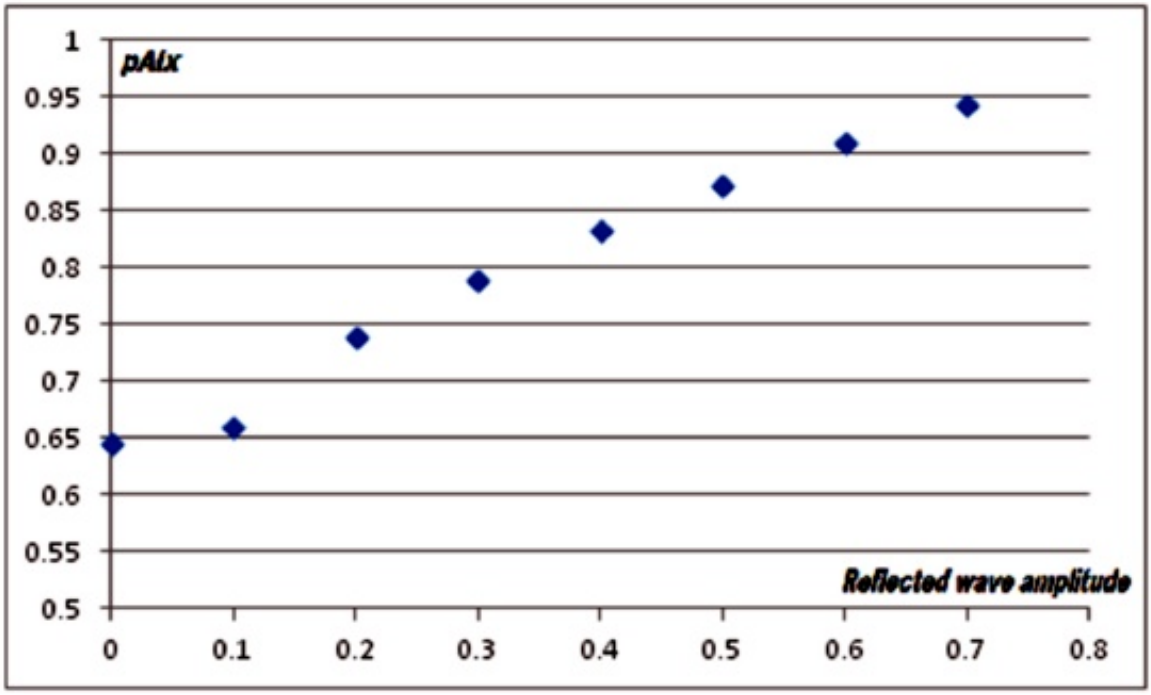

Figure 2 Simmulation results for the dependence of peripheral augmentation index respect to amplitude of the refected wave.
Amplitude of the incident wave was set =1.

When fixing the amplitude of the reflected wave at 0.3 times the amplitude of the incident wave, a nonlinear dependence of AIx respect to wave velocity is obtained for the velocity range from 4 to 17 m/s (figure 3).

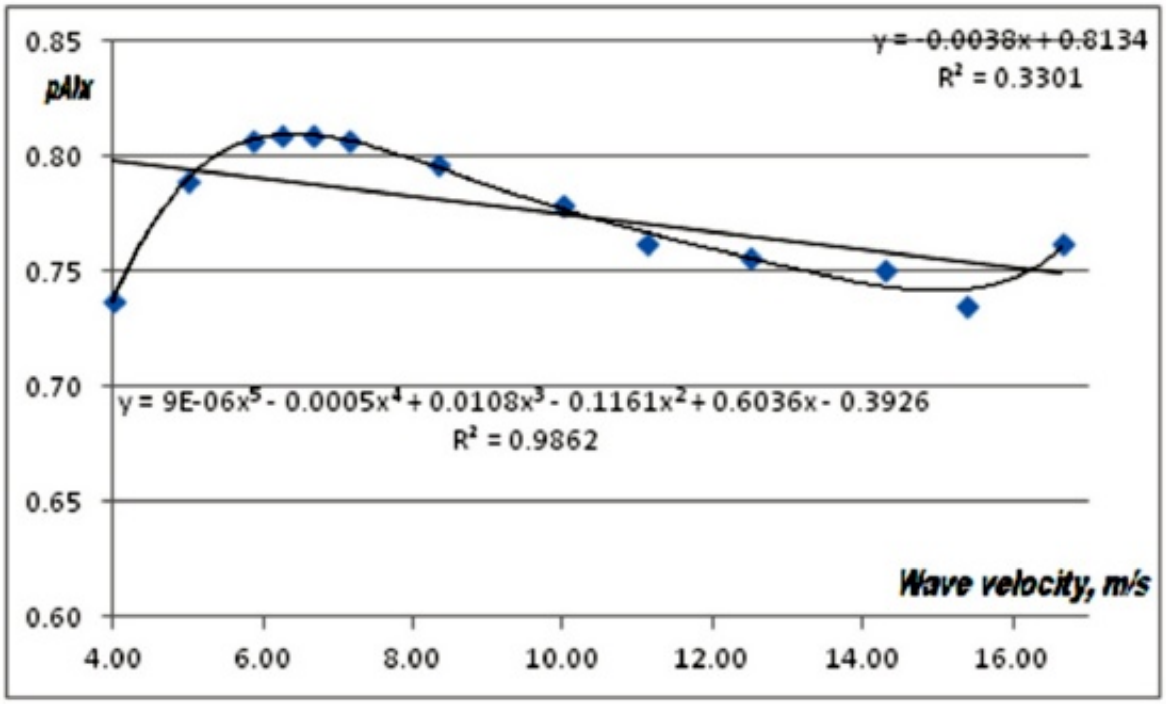

Figure 3. Simmulation results for the dependence of peripheral augmentation index respect to wave velocity.
Linear fit shos a tendency to reduction as velocity increases, whereas a 5th degree polynomial fit suggest a nonmonotonous dependence.

As apparent from figure 3, depending on the velocity range AIxcan either increase (e. g. from 4 to 6 m/s or from 15 to 17 m/s)) or decrease (from 7 to14 m/s) of remain almost unchanged (from 5 to 7 m/s). The general trend for the whole range of velocities is decreasing. Even when these numerical experiments cannot be taken at "face value" they can provide a good explanation for the observed decrease of AIx with age.

Thus far, this is the first report of a negative correlation between pAIx and age. The used data sample is characterized by a very homogenous ethnic and cultural origin (mostly citizens from Orense, a city at the heart of Galicia having a low rate of inmigrantion. Ethnic differences have been documented for AIx developmental equations[7]. However, this cannot be the only factor for the obtained results. At any rate, a brief review of literature can suggest that the claim about a positive correlation between AIx and age does not enjoy a great support. Thus some authors claim that the correlation is strongest for ages below 50 years, vanishing for older ages[8-9]. Moreover, some authors have hypotesized a decreasing wave reflection in older persons[10]. On the other hand, some authors have found a negligible role of AIx as a surrogate for arterial stiffness under adrenergic estimulation[11]. In other studies, multivariate analysis has found no correlation with age for AIx[12].

Working with rabbits, it was found a non-significant correlation between Aix and age. Moreover, as arteriosclerosis progressed and arteries stiffened, this did not affect the AIx[13]. Similar results were obtained in humans[14-15].

In another report[4] it was found that age significantly correlated with augmentation index only in healthy subjects but not in those with atherosclerotic disease. Additionally those authors found that augmentation index is not correlated with the presence of vasoactive medication in subjects without atherosclerotic disease.

It is not excluded that the inverse relation reported between AIx and height is an indirect consequence of an increase in AIx after an increase in time shift for the reflected wave, as documented from our simulations.

Such diversity of results can put in doubt the validity of this index as a marker of cardiovascular function. Results of our simulations can at least partially explain this diversity of results. As shown in figure 3 depending on the range of pulse waves to be regarded, the relationship between AI and arterial stiffness can be either positive, negative or nil.

The European Society of Cardiology-European Society of Hypertension guidelines of the year 2007 attribute to consequences of arterial stiffness and wave reflection a major role on cardiovascular mortality[16]. But the authors claimed the "poor availability of devices and methods providing easy and widely suitable measuring of arterial wall stiffness or their surrogates like augmentation index (AIx)". However, our results are not supportive of AIx being a good candidate for such a role. Particularly, it seems that the validity of AIx as a vascular index needs more substantial support; it is not excluded that other new indices are required for assessing vascular function and its decline with age and pathological condition.

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Letters to the Editor / Cartas al Editor

RENAL FUNCTIONAL EQUATIONS: THEIR EVOLUTION AND ROLE IN CKD PATIENTS

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To the Editor:

Traditionally, glomerular filtration rate (GFR) has been identified as the best marker of global renal function, calculated by using substance clearance techniques such as inulin or creatinine aided with cimetidine[1]

Chronic kidney disease (CKD) is a syndrome which derives from a progressive and generalized deterioration of renal function secondary to nephronal mass destruction, and renal functional evaluation is very important for doing its diagnosis and follow up[2,3]. However, since all clearance techniques have some degree of difficulty, an easier way of determining GFR, equations to estimate glomerular filtration have been developed. In the present review article we analyzed which was the evolution of these renal functional equations, and which is their role in CKD patients.

In order to have an easier way of determining GFR, equations to estimate glomerular filtration have been developed, most of them mainly based on serum creatinine (Table 1).

Kampmann et al.[4], Cockcroft and Gault[5] and Rowe et al.[6] described renal function formulas for estimating GFR in the clinical practice. Cockcroft and Gault's formula (1976) is the most frequently used, although it has been questioned due to the fact that it exaggerates the decline in GFR, at least in people older than 80[4-7]. However, Nicoll et al. found a good correlation in 18 individuals of ages between 66 and 82 using eGFR calculated according to Cockcroft and Gault's formula and the one obtained with 99Tc-DTPAm[7].

One of the problems that appeared when interpreting such studies was that they did not use individuals who represented the population well. Rowe et al. examined healthy old people in the community, while Kampmann et al.[4] used hospital population excluding those patients with high levels of creatinine in blood in comparison with healthy adults. Cockcroft and Gault[5] used hospitalized patients for their study, without excluding anyone regardless of their renal function[3-5].

In 1987 Keller[8] pointed out that the simplest formula to estimate GFR for people between 25 and 100, with normal creatinine values, is: [130-age (in years) ml/min]. In the last 20 years other formulas have been developed to predict glomerular filtration using indirect calculations and serum creatinine as a starting point, such as Nankivell's[9], and Baracskay's[10] (Table 1)[7-10].

Table 1: Different formulae to estimate glomerular filtration rate using demographic and analytic as starting points.

Year	Author	GFR Formula (ml/min/1,73 m^2)
1973	Jellife	GFR=98-[0.8x (age-20)/ Serum Creat. x (body mass/1.73) x [0.9 if a woman]
1974	Kampmann	GFR=Cre. In urine x weight x 100 / Serum Cre.
1976	Rowe	GFR=133 – 0,64 x age
1976	Cockcroft	GFR=(140-age)x weight (x 0,85 if a woman) / (Serum Creat.x 72)
1987	Keller	GFR=130 –age
1993	Walser	GFR=7.57 x (Serum Cre.mmol/L)$^{-1}$ -0.103 x age + 0.096 x weight $^{-6.66}$
1995	Nankivell	GFR=6,7/Serum Cre.(mmol/L) + 0.25 x weight – 0.5 x urea -0.01 x height^2 + 35 (25 if a woman).
1997	Baracskay	GFR=1/2[100/Serum Cre.]+88 – age
1999	MDRD	GFR=170 x [Serum Cre.$^{]-0,999}$ x [age]$^{-0,176}$ x [0,762 if a woman]x [1,180 if an african american] x [BUN]$^{-0,170}$ x
2004	MDRD-4	GFR=186.3 x [Serum Cre.]$^{-1,154}$ x [age]$^{-0,203}$ x [0,742 if a woman] x [1,142 if an african american]
2005	MDRD-IDMS	GFR = 175 x (creatininE/88,4)$^{-1,154}$ x (age)$^{-0,203}$ x (0,742 if a woman) x (1,210 if black)
2007	MDRD-6	eGFR= 170 x (creatinine/88,4) $^{-0,999}$ x (age) $^{-0,176}$ x (urea x 2,8) $^{-0,170}$ x (albumina/10) ^{0,318} x (0,762 if a woman) x (1,180 if black)
2009	CKD-EPI	eGFR = 141 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{edad} × 1.018 [if a woman] where Scr is serum creatinine, k is 0,7 for women and 0,9 for men, α es - 0,329 for women and -0.411 for men.
2010	DAF	GFR= 80 / Serum Creat. (70 if a woman)

In 1999, with the aim of being more precise regarding glomerular filtration, the MDRD group (The Modification of Diet in Renal Disease) published a new equation to estimate GFR based on creatinine clearance and the concentration of serum creatinine taking into account the demographic and clinical characteristics in patients previously diagnosed with CKD. However, this equation has not been proven in people without renal disease, people with type 1 and 2 diabetes in treatment with insulin, people younger than 18, old people (older than 70), pregnant women, patients with comorbidities and transplant recipients[11].

In 2001 Lewis et al.[12] recalculated the formula, adding renal transplanted and Afro-American patients with nephrosclerosis. However, neither of the formulas were applied to subgroups: healthy, diabetic and people older than 70. Therefore, such equations are not valid for the general population. Despite all these findings, patients who have a moderate GFR reduction between 30 and 59 ml/min/1.73 m^2, are still considered in the CKD threshold. If we take into consideration this criteria for diagnosing CKD, by eGFR < 60 ml/min/1.73 m^2, it would incorrectly indicate that approximately 17% of people older than 60 would suffer from CKD [11-13].

In 2009 the CKD-EPI formula was created with the aim of obtaining more reliability for the calculation of eGFR based on the levels of creatinine in blood, but despite the fact that it is more reliable and accurate than MDRD, it appears to have important limitations regarding the representation of the population and, particularly, since it does not have a significant sample of people older than 70 years[14].

In any case, when we use the formulas or tests based on serum creatinine values we should take into account that such values per se are not an optimal marker of GFR. There are well documented data which point to the fact that serum creatinine values can vary significantly in multiple scenarios such as the patient´s metabolic state, their muscle mass, states of hyper or dehydration, some medication (cimetidine) and tubular handling (creatinine backfiltration). All these factors could cause errors in those formulas which use the concentration of serum creatinine to estimate GFR[14-16].

As we can appreciate in Table 2, there are significant differences in a GFR value when it is obtained using creatinine clearance, Cr51-EDTA and the MDRD formula. It can be identified, at the end of the table, that two 80 year old males with the same serum creatinine have substantially different glomerular filtration rates depending on the method used. As both men are the same age and have the same serum creatinine, they have the same GFR value calculated with the MDRD (98.8 ml/min/1.73m^2) formula. If we use creatinine clearance instead of MDRD, one of them has a GFR of 99 ml/min/1.73m^2, while the other only reaches a value of 56.3 ml/min/1.73m^2.

It is worth noting that the difference between these two healthy old men is in the elimination of urinary creatinine: 120 mg/dL in one and 65 mg/dl in the other. This phenomenon could be explained by creatinine backfiltration phenomenon already described

in aged people. It is also interesting to observe that both of them have a comparable GFR value (76 and 60 ml/min/1.73 m^2) when Cr51-EDTA is used. As a result the same person may be considered as affected with CKD or not depending on the method used to estimate GFR.

Table 2: Comparison of creatinine clearance using different methods on young and old individuals. De Macías Nuñez JF, García Iglesias C, Tabernero Romo JM, Bondía A, Rodríguez Commes JL, Corbacho L, Martin M, De Pablo F, De Castro S. [GFR study in healthy old people] Rev. Esp. Geriatr. y Gerontol. 1981;16(2):113-124

AGE	Gender	Serum Creatinine	Urine Creatinine	Ccr	Cr^{51}-EDTA	MDRD
14	V	0,8	70	152,72	102,48	140,83
25	V	0,9	55	79,51	114,73	109,28
27	V	0,8	305	102,27	100,34	123,25
32	V	1	175	125,42	95,3	92,04
38	V	0,8	45	126,7	81,83	114,99
42	H	0,7	40	121,53	101,9	97,53
46	V	0,8	138	115,66	86,53	110,61
48	V	0,8	80	132,53	128,45	109,66
52	V	0,8	185	165,27	96,72	107,89
68	V	0,9	118	105,94	83,51	89,19
71	H	0,8	72	84,39	85,38	75,15
72	V	1	85	75,14	89,04	78,07
73	H	0,7	70	83,12	75,99	87,18
73	V	0,8	120	69,64	68,42	100,71
73	H	1	70	79,07	75,99	57,76
74	V	0,9	50	142,32	78,54	87,67
78	V	1	85	63,99	80,71	76,81
79	V	0,9	112	89,18	85,61	86,52
80	**V**	**0,8**	**120**	**99,4**	**76,05**	**98,86**
80	**V**	**0,8**	**65**	**56,32**	**60,55**	**98,86**

AGE: in years, **V:** male, **H:** female,
Serum creatinine normal value: 0.9 ± 2 mg/dl,
Ccr: creatinine clearance (ml/min/1.73 m^2)

There are many difficulties regarding the recommendation of basing CKD diagnosis just on a eGFR critical value, not taking into account other variables such as age, gender, race, renal disease etiology, and associated pathologies[17, 18].

For instance, in stage 3 - CKD (GFR between 30-60 ml/min/1.73 m^2), even though a diagnosis has been established by documenting eGFR < 60 ml/min/1,73m^2 during a period longer than three months, it should be pointed out that this criteria does not necessarily apply to elderly people since GFR reduction can present as a consequence of normal ageing[17, 19].

Similarly, a petit vegetarian woman with eGFR < 60 ml/min/1.73 m^2, who has a very positive renal reserve (> 100 %), and is not suffering from any of the classically associated complications to CKD such as uremic symptoms, anemia, hyperphosphatemia, hypocalcemia, metabolic acidosis, hyperparathyroidism, altered urinalysis, and/or abnormal renal ultrasound, should not be considered a CKD patient[14, 20]

Even more, some authors do not support the idea of a eGFR < 60 ml/min/1.73 m^2 "critical value" as an independent risk factor to develop CKD in the future. Firstly, according to what was published by Go et al., independent mortality factors do not increase with eGFR values between 45 and 59 ml/min/1.73 m^2 when chronic damage has been established from serial measurements of serum creatinine[21]. Secondly, a decrease in mortality risk in people older than 45 has been demonstrated, with a GFR between 50 to 59 ml/min/1.73 m^2 when chronic damage is established in a period of 3 to 6 months[22,23]. Thirdly, the PREVEND study shows that approximately two thirds of the patients in stage 3 - CKD do not present albuminuria and their risk of cardiovascular complications, according to the tables adjusted by age and gender, were similar to those people who did not present renal disease[23].

Another problem related with performing CKD diagnosis based on eGFR is that the obtained CKD prevalence data is exceedingly variable depending on the applied formula[24-27]. In this sense, the EPIRCE study (2010) found a global prevalence of CKD in stages 3 to 5 (according to the NKF-K/DOQI recommendations with eGFR < 60 ml/min/1.73 m^2) of 6,8%, increasing this number to 21,4% in people older than 64[24]. In the EROCAP study (2007), the prevalence of CKD was studied with the same criteria of eGFR < 60 ml/min/1.73 m^2 obtained in 9233 patients older than 18 who attended a primary health care consultation. According to its results, global prevalence varied depending on the eGFR formula used, between 21,3% and 22.7% while in the population older than 70 it reached 33,7%[28,29].

In 2008 Zhang and Rothenbacher conducted a systematic review of 26 studies on the prevalence of CKD in different geographical areas of the world[29]. Respecting the same estimation criteria as glomerular filtration, the CKD diagnosis and values which were < 60 ml/min/1.73 m^2, resulting in a global media prevalence in the adult population older than 30 of 7,2% while in people 64 or older it varied between 23,4% and 35,8%[29,30]. Then, it seems that eGFR formulas are much more helpful in CKD staging and follow up, than in its diagnosis.

In order to avoid diagnostic errors like the above mentioned one, a new formula has been developed for diagnosing CKD: HUGE formula. It does not take into account patient´s eGFR for diagnosing CKD but two biochemical variables, and a clinical one: hematocrit, uremia, and gender. This formula is as follows

HUGE = 2.505458 - (0.264418 x Hematocrit) + (0.118100 x Urea) [+ 1.383960 if male], where a value > 0 diagnoses CKD.

HUGE formula allows for the discrimination between a healthy old person (HUGE<0) and a CKD patient (HUGE>0), both with similar eGFR, with high sensitivity and specificity, especially in people older than 70[31,32].

In conclusion, according to the aforementioned considerations, we should state that glomerular filtration estimations, in particular those obtained with the MDRD formula or the CKD-EPI formula are, undoubtedly, valid to stage and follow up on the progress of patients already diagnosed with CKD. However, the use of eGFR lower than 60 ml/min/1.73 m^2 to follow up on patients without a known diagnosis is not only controversial but also perhaps not recommended.

On the other hand, to establish an incorrect diagnosis of CKD using estimations of GFR which are lower than 60 ml/min/1.73 m^2 obtained through routine lab tests could be considered arbitrary, insufficient and especially inadequate in the old population (older than 70).

Conflict of interests: The authors declare not to have conflict of interests in this study

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