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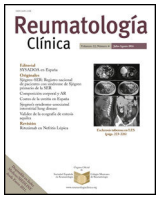

Original article

An update on the study of synovial fluid in the geriatric patient

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ABSTRACT

Background: The characteristics of synovial fluid (SF) in geriatric patients differ from those in younger patients. In Mexico, epidemiologic data on the incidence of different rheumatic diseases in geriatric patients are scarce.
Objective: To describe the physical characteristics of geriatric SF and the prevalence of crystals in knee and other joint aspirates from patients with previously diagnosed joint disease.
Materials and methods: A retrospective study was performed with a baseline of 517 SF samples between 2011 and 2023. White blood cell count was performed by Neubauer chamber and crystals were identified by polarized light microscopy. Descriptive statistical analysis was performed and prevalence was reported as a percentage.
Results: The mean age of the adults was 73.5 ± 5.0 years, 54.4% were women and 45.6% were men. The mean SF volume was 6.3 ± 9.5 mL in older adults and 15.3 ± 24.9 mL in those younger than 65 years. The mean viscosity in older adults was 9.5 ± 4.5 mm and the mean leukocyte count was 7352 ± 16,402 leukocytes/mm^3. Seventy percent of the older adults' SFs were referred to the laboratory for osteoarthritis (OA), with lower proportions for rheumatoid arthritis (RA) (14.6%) and gout (5.1%). Of the crystals observed in the geriatric population, 14.6% corresponded to monosodium urate crystals (CUM) and 18.9% to calcium pyrophosphate crystals (CPP).
Conclusions: The characteristics of LS in older adults were smaller volume, increased viscosity, and non-inflammatory. The main diagnoses were OA, RA, and gout. The crystal content of the SF of the geriatric population corresponded mainly to CPP.

Panorama actual del estudio de líquido sinovial en el paciente geriátrico

Palabras clave:
Líquido sinovial
Ancianos
Población geriátrica
Cristales
Osteoartritis
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RESUMEN

Antecedentes: Las características del líquido sinovial (LS) en pacientes geriátricos varían en comparación con pacientes más jóvenes. En México, los datos epidemiológicos sobre la incidencia de diversas enfermedades reumáticas en el paciente geriátrico son escasos.
Objetivo: Describir las características físicas del LS geriátrico y la prevalencia de cristales en aspirados de rodilla y otras articulaciones de pacientes con enfermedades articulares previamente diagnosticadas.
Materiales y métodos: Se realizó un estudio retrospectivo con una base de 517 muestras de LS entre 2011 y 2023. El recuento de glóbulos blancos se realizó con cámara de Neubauer, y los cristales se identificaron por microscopia de luz polarizada. Se realizó un análisis estadístico descriptivo y la prevalencia se reportó como porcentaje.

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Resultados: La edad promedio en los adultos fue de 73,5 ± 5,0 años; el 54,4% fueron mujeres y el 45,6%, hombres. El volumen promedio del LS en adultos mayores fue de 6,3 ± 9,5 ml, mientras que en menores de 65 años fue de 15,3 ± 24,9 ml. La viscosidad promedio fue de 9,5 ± 4,5 mm en los adultos mayores, y una cuenta de 7.352 ± 16.402 leucocitos/mm^3. El 70% de los LS de los adultos mayores fueron remitidos a laboratorio por osteoartritis (OA), u una proporción más baja, por artritis reumatoide (AR) (14,6%) y gota (5,1%). En cuanto a los cristales observados en los LS de la población geriátrica, el 14,6% correspondieron a cristales de urato monosódico (CUM) y el 18,9%, a cristales de pirofosfato de calcio (CPP).
Conclusiones: Las características del LS en los adultos mayores fueron menor volumen, viscosidad incrementada y no inflamatorios. Los principales diagnósticos fueron OA, AR y gota. El contenido de los cristales en los LS de la población geriátrica correspondió principalmente a CPP.

Introduction

All countries in America are facing a common demographic transition related to longevity, declining fertility rates, and changes in family lifestyles. Recent demographic data indicate that Mexico is undergoing a geriatric transition in terms of the ratio of young people to older adults.[1] Although Mexico's population is relatively young, with a median age of 27.9 years in 2015, it will age rapidly in the coming years, increasing to 42 years by 2050. The rapid increase in the country's median age also reflects the growing proportion of people aged 65 and older, which is expected to triple to 20.2% by 2050.[2] Mexico is the eleventh largest country in the world in terms of population density and area. A large young population is giving way to a growing elderly population that will inevitably create demands for health care and social security. As a result, Mexican seniors often continue to work well into old age. From a chronological point of view, the medical treatment of the elderly (geriatrics) begins at 65 years of age; however, this is currently not an adequate definition of an elderly patient and not the reason to be treated by a geriatrician. In addition to chronological age, other factors should be considered, such as: reduced functional reserves and frailty, pathophysiological defined by a subclinical inflammatory state.[3]

The term "aging" refers to various physiological changes from adulthood to death. As part of these transformations, bones remodel throughout life as older bone tissue is replaced by new bone tissue. This systematic remodeling provides a balance between bone resorption and new bone formation that maintains skeletal integrity.[4] It is well documented that aging is a major contributor to the development of osteoarthritis (OA) of the hands, hips, spine, and knees. The mechanisms responsible are diverse and may include an age-related proinflammatory state. Age-related inflammation can be both systemic and localized.[5] Age-related changes in certain tissues, resulting in increased production of cytokines such as interleukins (IL)-6, IL-7, IL-1β and TNFα, may promote systemic inflammation. Numerous studies have demonstrated an age-related increase in IL-6, which has been associated with decreased physical function, frailty, and an increased risk of progression of knee osteoarthritis.[6,7]

The characteristics of synovial fluid (SF) in geriatric patients may differ from those of younger patients. SF lubricates the joints to ensure smooth movement, and in young, healthy joints, it has greater amounts of high-molecular-weight hyaluronic acid (HA) molecules between 2000 and 10,000 kDa that provide lubrication.[8] As people age, the size of the HA molecules decreases, reducing their ability to function as shock absorbers and lubricants.[4,9,10] Also, a decrease in the amount of SF, and with it a higher concentration of proteins, which may be associated with chronic inflammatory and oxidative processes in geriatric patients.[11] In terms of crystal deposition, aging increases the likelihood of developing diseases such as gout. Some studies have shown that crystals of both monosodium urate (MSU) and calcium pyrophosphate (CPP) become more common with age.[12] Observational studies suggest that age, rather than OA itself, is the predominant factor favoring progressive pathological calcification of articular cartilage,[13] although there are studies suggesting that mineralization is a result of OA and not merely age-related, as no correlation was found between patient age and the amount of matrix mineralization in an older adult population studied.[14]

In a population under 65 years of age studied in the United States, men have a four times higher prevalence of gout than women; however, this ratio decreases to 3:1 for men to women over 65 years of age.[15] In the United Kingdom, the prevalence of gout was found to be about 2% in men and about 1% in men and women combined, but the highest prevalence occurred in people aged 75–84 years; particularly in men of this age, with an incidence of gout of about 8%.[16] The prevalence of gout increases in direct relation to age; therefore, the increased longevity of populations in developed countries may contribute to a higher prevalence of gout through association with age-related diseases (e.g., metabolic syndrome and hypertension) and treatments for age-related diseases.[17]

These characteristics may be common in certain geriatric patients with rheumatologic diseases, but they may vary according to their health or disease status. In Mexico, there is a lack of epidemiological studies in older adult population that characterize this sector of the population, therefore, it is of vital importance to be able to provide an overview in relation to this sector of the population, so the objective of this study was to define the characteristics of the SF of geriatric patients and also make a comparison with a middle-aged group, to address the growing public health burden of various rheumatologic diseases in older adults.

Materials and methods

A retrospective study was performed using a database generated in the Synovial Fluid Laboratory, which included the results of SF analysis of 517 samples collected from patients who attended the Hip-Knee Joint Replacement Service and the Rheumatology Department of the reference hospital Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra (INRLGII) between January 2011 and July 2023. Based on clinical examination, a diagnosis was assigned to each patient prior to SF analysis. A database was developed in which we considered SF results, age, sex, and diagnosis from the electronic records of the patients' files. Patients were stratified into those younger than 65 years and those older than 65 years. Macroscopic features of SF included volume, color, clarity, and viscosity using the "drop test," employing a syringe. Observing the length of the string produced by the SF.[18] Microscopic analysis of SF included total white blood cell (WBC) count and crystal analysis. SF analysis was at the physician's request and performed by two operators with previous experience in SF analysis using conventional techniques. The total WBC count was evaluated using a Neubauer counting chamber and classified according to the American College

Table 1
General description of the study population and characteristics of the SF samples collected during the 2011–2023 period.

Parameter	Total (n = 517)	<65 years (n = 304)	≥65 years (n = 213)	P
Age in years ± SD	57.1 ± 15.6	49.5 ± 12.7	73.5 ± 5.0	**<0.001**[b]
Gender				
Female, *n* (%)	276 (53.4)	160 (52.6)	116 (54.4)	**0.02**[a]
Male, *n* (%)	241 (46.6)	144 (47.4)	97 (45.6)	
SF volume (mL) ± SD	12.0 ± 20.8	15.3 ± 24.9	6.3 ± 9.5	**0.003**[b]
Viscosity (mm) ± SD	8.84 ± 5.6	8.5 ± 6.0	9.5 ± 4.5	0.463[b]
WBC (10^3/mm^3) ± SD	13,985 ± 25,940	18,016 ± 29,786	7352 ± 16,402	**<0.001**[b]
Studied joint				
Knee, *n* (%)	473 (91.5)	283 (93.1)	190 (89.2)	**0.008**[a]
Elbow, *n* (%)	16 (3.1)	11 (3.6)	5 (2.3)	
Ankle, *n* (%)	5 (1.0)	4 (1.3)	1 (0.5)	
Hip, *n* (%)	2 (0.4)	2 (0.7)	0 (0.0)	
Hand, *n* (%)	5 (1.0)	2 (0.7)	3 (1.4)	
Shoulder, *n* (%)	8 (1.5)	1 (0.3)	7 (3.3)	

P-values are expressed as mean ± SD.
[a] *P*-values estimated by chi-squared test, $\alpha = 0.05$.
[b] *P*-values estimated by Mann–Whitney *U* test, $\alpha = 0.05$. WBC, white blood cells. Significant *P*-values are shown in bold.

of Rheumatology guidelines.[19] Polarized and compensated light microscopy was used to identify crystals of MSU, CPP, cholesterol and others by morphology and birefringence.[19] The number of initial diagnosis modified upon SF analysis was identified employing number of SF samples received with or without presumptive diagnosis and how the diagnoses were modified after SF analysis. All participants signed a written informed consent letter. This study was carried out under the criteria established in the Declaration of Helsinki and was derived from a protocol with registration number INR-21/19, which was approved by the Ethics and Research Committee of the INRLGII.

Statistical analysis

Descriptive statistical analysis was performed. Prevalence was reported as a percentage with a 95% confidence interval (95% CI). For inferential statistics on epidemiologic variables, the Student's *t*-test was used for quantitative variables and the χ^2 test for qualitative variables, with a confidence level of $\alpha = 0.05$. The Mann–Whitney *U* test was used to compare groups that did not have a normal distribution. SPSS v20 (IBM, Chicago, IL) and PRISMA statistical software were used.

Results

Table 1 summarizes the main demographic and laboratory characteristics of SF in both study groups. The study population had a mean age of 57.1 ± 15.6 years and was stratified into two study groups: young population (<65 years) and older adult population (≥65 years); the former had a mean age of 49.5 ± 12.7 years and the older adults 73.5 ± 5.0 years, this difference was statistically significant ($P < 0.05$). Also, this population was characterized by being predominantly female (53.4%), while 46.6% belonged to the male sex. The distribution in the subpopulations was 52.6% female and 47.4% male in the population under 65 years of age. Among older adults, 54.4% were female and 45.6% were male. Regarding the characteristics of SF, reduced SF volumes of 6.3 ± 9.5 mL were obtained in the older adult population, while in the younger population it was 15.3 ± 24.9 mL. The SF were more viscous in the patients older than 65 years, with a mean viscosity of 9.5 ± 4.5 mm, compared to 8.5 ± 6.0 mm in the population younger than 65 years, however was not significantly. Regarding inflammation, the SF of adults older than 65 years had 7352 ± 16,402 leukocytes/mm^3, i.e. highly inflammatory, whereas adults younger than 65 years had 18,016 ± 29,786 leukocytes/mm^3, also highly inflammatory, but almost twice as many leukocytes as geriatric patients. In those <65 years the most studied joint was the knee (93.1%), elbow (3.6%), ankle (1.3%) and hip (0.7%). In those ≥65 years, the hand (1.4%) and shoulder (3.3%) were the most studied joints.

In relation to diagnoses, in the population under 65 years of age, 36.6% were due to OA, 26.9% RA, 17.9% gout, 3.1% reactive arthritis, as well as ligament injury and ankylosing spondylitis (AS). A smaller proportion were due to septic arthritis (SeA) and 7.6% to other causes (Fig. 1a). Seventy per cent of SFs in older adults were referred to the laboratory for OA, almost twice as many as in the population younger than 65 years, a smaller proportion were due to conditions such as RA (14.6%), diagnoses of gout were lower in this study group (5%), and for AS and SeA 2.2% each. Reactive arthritis and ligament injuries were conditions that were not identified in this part of the population (Fig. 1b).

According to the Kellgren–Lawrence (KL) radiographic scale, in the total population with a diagnosis of OA, 60.3% were grade 4, 38.1% grade 3, and only 1.6% grade 2. In the group aged < 65 years, 57.6% had KL = 4 and 42.4% KL = 3; in the group aged > 65 years, 63.0% had KL = 4, 33.3% KL = 3 and 3.7% KL = 2.

Distribution of crystals in the SF

In terms of crystal content, the young population was characterized by a higher overall crystal content, with at least one crystal identified in 93 samples. In the older adult SF, 81 samples contained at least one crystal type. In the group of adults younger than 65 years, MSU crystals were most frequently identified, as 14.6% corresponded to MSU, 11% CPP, 1% cholesterol, 0.7% lipids and 3.7% to glucocorticoids. Regarding the crystals observed in the SF of the geriatric population, 14.6% corresponded to MSU, 18.9% CPP, only one sample showed cholesterol crystals (0.5%), 1% were lipid crystals and 3.3% to glucocorticoids (Table 2). There were 2 cases with both types of crystals, MSU and CPP, males aged 62 and 76 years.

According to the result of the crystal analysis, in the total number of samples, 116 (22.4%) modified the initial diagnosis of remittance. By age group, in those younger than 65 years 48 (15.8%) modified the initial diagnosis, while for those older than 65 years, 68 (31.9%) modified it ($P < 0.001$).

The SFs in geriatric patients were non-inflammatory (69.0%) versus those younger than 65 (43.8%) years, respectively). For inflammatory SF, 46.1% were in patients younger than 65 years and 25.4% in geriatric patients. For infectious SF, 10.2% corresponded to patients younger than 65 years and only 5.6% to geriatric patients (Table 3).

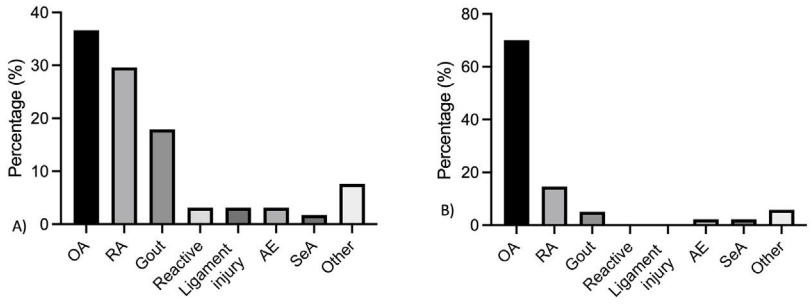

Fig. 1. (A) Prevalence of diagnoses in patients < 65 years old. (B) Prevalence in adults ≥ aged 65 years old.

Table 2
Crystals distribution in the study population stratified by age.

Crystal	<65 years *n* = 302 (%)	≥65 years *n* = 212 (%)	χ^2	CI 95%	*P*
MSU			0.077	(0.99–0.99)	0.962
Yes	44 (14.6)	31 (14.6)			
No	258 (85.4)	181 (85.4)			
CPP			6.525	(0.024–0.033)	**0.038**
Yes	33 (11.0)	40 (18.9)			
No	269 (89.0)	172 (81.1)			
Cholesterol			0.516	(0.838–0.857)	0.773
Yes	3 (1.0)	1 (0.5)			
No	299 (99.0)	211 (99.5)			
Lipids			0.205	(0.99–0.99)	0.903
Si	2 (0.7)	2 (1.0)			
No	300 (99.3)	210 (99.0)			
Steroids			0.120	(0.99–0.99)	0.942
Yes	11 (3.7)	7 (3.3)			
No	291 (96.3)	205 (96.7)			

P-values were estimated with the Chi-square test, $\alpha = 0.05$. MSU, monosodium urate crystals; CPP, pyrophosphate crystals. Significant *P*-values are shown in bold.

Table 3
Status of inflammation of the SF in the study groups.

Classification	Total *n* = 517 (%)	<65 years *n* = 304 (%)	≥65 years *n* = 213 (%)	χ^2	*P*
Non-inflammatory	280 (54.2)	133 (43.8)	147 (69.0)	32.2	<0.001
Inflammatory	194 (37.5)	140 (46.1)	54 (25.4)		
Infectious	43 (8.3)	31 (10.2)	12 (5.6)		

Non-inflammatory < 200–2000 WBC/mm^3; Inflammatory > 2000–50,000 WBC/mm^3; Infectious > 50,000 WBC/mm^3. *P*-value estimated with the Chi-square test, $\alpha = 0.05$.

Discussion

The characteristics that stood out in the SF of the geriatric population were a significantly lower volume with a slight increase in viscosity, this last parameter without becoming significant, however, it is known that the degradation of high molecular weight HA occurs under an inflammatory and/or oxidative stress environment, affecting the deterioration and loss of its viscoelastic properties of the SF.[20] Low molecular weight HA exerts different biological activities compared to high molecular weight HA. HA chains of 25–50 disaccharide units are inflammatory, immunostimulatory and strongly angiogenic.[21] Regarding the prevalence of different rheumatic diseases, we found that the most common pathology was OA (41.0%), followed by RA (18.7%) and gout (15.5%). By age group, 70.1% of adults older than 65 years had OA. A previous study in a Mexican population reported a prevalence of OA of 20% in a group of participants over 40 years of age using clinical criteria for OA, while the prevalence of OA using radiologic criteria was 25%, although the mean age of the population was 57.4 ± 10.9 years. On the other hand, in the age group 61–80 years, the prevalence of OA was 31.4%.[22] Considering our total population, the prevalence of OA in those older than 65 years was 18.56%. Similarly, Pelaez-Ballestas et al.[23] reported a prevalence of OA of 10.5% in the general population of Mexico, and in those over 50 years of age, the prevalence was 11%, lower than the prevalence we found in our study. However, this Mexican study used the COPCORD methodology to report the prevalence in five Mexican regions, and our study was based only on radiologic and clinical diagnosis.

The prevalence of OA varies depending on the definition of OA, the joints involved, and population characteristics. In the study by Zhang et al.,[24] the age-standardized prevalence of radiographic knee OA in adults ≥ 45 years was 19.2% in the Framingham Study and 27.8% in the Johnston County OA Project. In the Third National Health and Nutrition Examination Survey in Mexico, approximately 37% of participants > 60 years of age had radiographic knee OA. Age is one of the strongest risk factors for OA of any joint. The increase in prevalence and incidence of OA with age is likely a consequence of cumulative exposure to biological changes such as cartilage thinning, muscle weakness, obesity, and oxidative damage.[24]

For RA, we found a prevalence of 18.7% in the general population and 14.6% in the population > 65 years of age, known as elderly-onset RA (EORA). Whether these patients developed symptoms

after > 65 years or were follow-up patients is not known. The annual incidence rate of EORA can vary widely depending on gender and country of origin. According to the Norwalk Arthritis Research Database in the United Kingdom, the incidence of RA increases with age. Compared to young-onset RA, the female-to-male ratio in EORA is reduced from 4:1 to 2:1.[25] In addition to incidence, some parameters found to be altered in RA in older adults are ESR and CRP, as well as IL-6, but not IL-1β and IL-8.[6]

The diagnosis of gout in our overall population was 15.5%, the same as when categorized by age, those younger than 65 years had a diagnosis of gout of 17.9% versus 5.1% in older adults. In a comparative study of 778 patients with gout, 57.7% were <40 years of age and 42.3% were >40 years of age.[26] Also, a recent epidemiologic report indicated that the prevalence of gout ranges from 1 to 4% worldwide, while the incidence ranges from 0.1 to 0.3%. However, both increase with each decade of life, with the prevalence increasing from 11% to 13% and the incidence increasing by 0.4% in people over the age of 80.[27,28] Although the prevalence of gout in our study was higher in the younger adult group, a United States study reported that gout disproportionately affects adults over the age of 65. The incidence from middle age to 65 years was 8.6% in men and 2.5% in women, while at 75 years the incidence was 11.8% and 5.0%, respectively.[29]

Regarding the distribution of crystals by age group, we did not observe any differences for MSU crystals in our study, as 14.6% of MSU corresponded to samples from young patients and another 14.6% to samples from the older adult group. However, CPP crystals were more prevalent in the older adult population than in those under 65 years of age (18.9% vs. 11%, respectively). This is in agreement with that reported by Heseldem and Freemont[30] who examined 6983 SF-containing crystals and found CPP in 53%, MSU in 44.5%, and both in 2.5% of the samples. The latter cases were considered mixed crystal arthropathy. These patients were 77% male and 23% female, and the highest incidence was found in patients between 76 and 80 years of age.

The majority of patients with CPPD were over the age of 65, with 30–50% of patients over the age of 85. A cross-sectional study of 2157 cases of calcium crystal deposition disease (CPPD) in United States veterans reported a point prevalence of 5.2 per 1000, with a mean age of 68 years and a 95% male prevalence. CPPD rarely occurs in patients younger than 60 years[31]; however, in our study the cases in which CPP was found were older adults diagnosed with OA, so one of the major problems for epidemiologic studies of CPPD is related to the challenges of diagnosis.[32] Although the exact incidence and prevalence of CPPD are still unknown, it is considered one of the most common chronic arthropathies, characterized by a prevalence that increases with age and can reach up to 13% in the elderly, depending on the joints evaluated and the tool used. Epidemiological studies have shown an increase in the prevalence of CPPD, which is related to age: 15% prevalence in patients aged 65 to 74 years, 36% prevalence in patients aged 75 to 84 years, and 50% prevalence in patients older than 84 years.[33]

Regarding SeA, we found a prevalence of 2.2% in the adult population, vs 1.7% in patients younger than 65 years, which is consistent with the report by Haag et al.,[34] who found that SeA is predominantly found in older adults, although a low proportion in children. SeA is more common in women than in men and usually occurs between the ages of 40 and 60, with a higher likelihood of occurrence after the age of 65. Mortality from SeA in geriatric patients is also higher than in the younger population.[35] Wu et al.[36] compared cohorts with SeA and the majority of geriatric participants were in the 65–74-year subgroup (53%). Reactive arthritis and ligament injuries were not identified in this population, as ligament injuries are more commonly associated with the young adult population.[37]

Regarding inflammatory status, inflammation was not observed in 69% of SF corresponding to the older adult population. However, inflammatory fluids were concentrated in the majority of patients under 65 years of age (46.1%), which is consistent with the diagnoses with which the SF analyses were initially associated. The WBC count in SF is a tool that contributes to diagnostic information and allows differentiation between inflammatory and noninflammatory diseases[38] and the "extent" or "degree" of any inflammatory process present to be assessed.[39] In SeA cases, SF should be sent for culture or in cases of diagnostic doubt.[40] Pal et al.[41] recommend discontinuing SF as a routine test since cell counts generally reflected known underlying diagnoses of inflammatory arthritis or OA. Routine SF analysis does not contribute to diagnosis or management in established rheumatic disorders and should be performed only when the underlying cause is uncertain or in newly presenting patients. We differ from this recommendation because according to our result, in the total number of samples, 22.4% modified the initial diagnosis of sending. By age group, in those <65 years 15.8% modified the initial diagnosis, while for those >65 years, 31.9% modified it. In addition to microcrystal detection, joint-fluid analysis has other uses. It can help to diagnose other forms of arthritis, including SeA. At present, joint-fluid analysis is even more necessary in patients with polyarthritis or spondyloarthritis treated with biological agent.[42]

SF analysis is a fundamental tool for identifying and aiding in the diagnosis and management of rheumatologic diseases such as RA, OA, gout and other joint diseases in geriatric patients, in therapeutic decision-making and in the interest of personalized medicine.

Conclusion

SF in older adults were characterized by decreased volume, a slight increase in the viscosity, and lack of inflammation. The main diagnoses for which SF were analyzed in older adults were OA, RA, and gout. Reactive arthritis and ligament injuries were conditions that were not identified in this population. The content of crystals in the SF of the geriatric population corresponded mainly to CPP. The SF study can provide valuable information about the joint health status of the elderly.

Authors' contributions

YZC and JFT conceived the idea for the study and developed the overall plan. YZC and JFT wrote the manuscript and performed the statistical analysis. VIS, CALP and REM collected the SF samples. YZC and JFT analyzed the SF samples. KMF developed the database. All authors reviewed and approved the final version of the manuscript.

Declaración de la IA Generativa y las tecnologías asistidas por IA en el proceso de escritura.

Statement: Durante la preparación de este trabajo los autores utilizaron DeepL y DeepL Write a fin de traducir y mejorar la redacción. Tras utilizar dicha herramienta, los autores revisaron y editaron el contenido según necesidad, asumiendo la plena responsabilidad del contenido de la publicación.

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Conflict of interest

The authors declare that they have no conflict of interest.

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