J Sex Gender Specif Med 2025; 11(1): 3-12

Gender difference in clinical response to viscosupplementation in hip osteoarthritis

Nazzareno Iannarelli[1], Umberto Massafra[2], Francesca Giovannangeli[2], Francesca Maggiolini[3], Raffaele Saporito[4], Luca Saccone[5], Antonio De Vito[6], Patrizia Amato[7], Alberto Migliore[1]

[1] Department of Medical and Surgical Specialties and Dentristy, University of Campania "Luigi Vanvitelli", Naples, Italy; [2] Rheumatology Unit and Research Center, San Pietro Fatebenefratelli Hospital, Rome, Italy; [3] Physiatry Departmental Operation Unit, San Pietro Fatebenefratelli Hospital, Rome, Italy; [4] Department of Clinical Pathology, San Pietro Fatebenefratelli Hospital, Rome, Italy; [5] Department of Orthopaedic and Trauma Surgery, San Pietro Fatebenefratelli Hospital, Rome, Italy; [6] Department of Internal Medicine, San Pietro Fatebenefratelli Hospital, Rome, Italy; [7] Gender medicine outpatient clinic dedicated to rheumatology, Health District 60, Local Health Authority (ASL), Salerno, Italy

Received 19 June 2024; accepted 15 November 2024

Summary. *Introduction.* Viscosupplementation (VS) is an available treatment for patients experiencing chronic pain from osteoarthritis (OA). Limited research exists on gender differences in pain reduction and functional improvement following hyaluronic acid (HA) injections. This study aims to present gender-based efficacy data of ultrasound (US)-guided HA injections in a substantial cohort of patients with hip OA. *Methods.* This retrospective, observational, post-marketing study utilized data from the Antiage registry. Evaluations of pain via the visual analogue scale (VAS), the Lequesne index and non-steroidal anti-inflammatory drugs (NSAIDs) consumption were conducted biannually over a follow-up period lasting up to six years. Inclusion criteria included patients aged 18 or older with symptomatic hip OA lasting at least one year. All participants received biannual HA injections for six years, guided by US to ensure accurate placement. *Results.* The study included 1,655 patients grouped by gender, age and BMI. Significant reductions in pain VAS, Lequesne index, and NSAIDs use were observed across all groups from baseline through each follow-up. Women consistently had higher baseline scores, which persisted over time, except in the aged over 80 group, where no significant baseline differences were found. Statistically significant differences in baseline NSAIDs use were also noted, with women showing higher consumption. Response to VS was comparable between genders. *Discussion.* The study reinforces the effectiveness and safety of HA injections for both genders with hip OA. Although women had worse baseline scores, their response to treatment was parallel to that of men.

Key words. Gender differences, hip osteoarthritis, viscosupplementation, intra-articular injections.

Introduction

Osteoarthritis (OA) is a common degenerative joint disease that results in considerable pain, mobility restrictions, economic strain, reduced quality of life, and disability.[1] The primary risk factors include genetic predisposition, sociodemographic variables, metabolic disorders, joint trauma (e.g., fractures, strains, repeated stress), excessive joint loading. OA can be also secondary to rheumatoid arthritis, and gout. Numerous gender-specific differences have been explored in studies on OA.[2] Epidemiological studies have consistently shown a higher prevalence of radiographic knee osteoarthritis (ROA) in women compared to men starting from middle age.[3]

Gender differences in lower extremity alignment can influence disease progression and surgical outcomes.[4] Szilagyi's examination of 27 studies on the association between risk factors and knee osteoarthritis (KOA) identified notable sex-specific differences: higher body mass index (BMI), alcohol consumption, atherosclerosis, and elevated vitamin E levels were more prevalent in women, while high physical activity, soft drink intake and abdominal obesity were more common in men. Knee injury, hypertension and low step rate appeared to impact both genders similarly.[5]

Jason Beng Teck Lim evaluated postoperative outcomes following total knee replacement (TKR) for end-stage KOA by reviewing data from 214 men and 1,040 women. The study found that women had poorer preoperative knee flexion, Oxford knee score, and Knee society score (KSS), as well as lower scores on eight SF-36 subscores. However, women experienced greater improvements in the Oxford knee score and KSS at both 6-month and 2-year follow-ups, along with better recovery in SF-36 subscores related to social functioning and mental health after two years.[6]

Regarding intra-articular (IA) treatments, Zhao's review of 30 randomized clinical trials (RCTs) did not identify gender differences in the therapeutic efficacy of platelet-rich plasma (PRP), though higher-quality studies with larger sample sizes are needed for confirmation.[7] Conversely, Sanchez found that in a study of 418 KOA patients undergoing multiple PRP injections, women presented with more baseline pain but experienced greater pain relief compared to men, though PRP was effective across both sexes.[8]

Projections indicate that by 2050, the prevalence of hip OA will increase by 78.6% compared to 2020 levels, reaching an estimated 62.6 million cases. Between 1990 and 2020, age-standardized years lived with disability (YLD) rates increased by 6% among adults aged 70.[9] Battista's register-based study involving 14,610 patients with hip or knee OA reported that women showed marginally better outcomes in terms of pain and function, although the differences were not clinically significant.[10]

Deng's investigation involving 4,796 KOA patients assessed gender differences in the relationship between patellofemoral grinding and synovitis using MRI at baseline, 12, and 24 months. The findings indicated that patellofemoral grinding was significantly associated with synovitis, with this correlation being more pronounced in women.[11]

Viscosupplementation (VS) is a common treatment for OA; however, data on gender differences following IA administration of hyaluronic acid (HA) remain limited. The purpose of our study is to evaluate and analyze gender differences in clinical outcomes after hip VS in a substantial cohort from the Antiage registry. The Antiage registry is managed by the National Association for IA Therapy of Hip Joint (www.antiagefbf.it), a non-profit organization comprising specialists in internal medicine, radiology, rheumatology, physical medicine and sports medicine, with expertise in US-guided IA therapy for hip conditions. The registry contains detailed records on patient characteristics, hip pathology, administered drugs, side effects, treatment outcomes, treatment courses and the total number of injections performed.

Patients and methods

Characteristics of the population under observation

Study design. This study is a retrospective, observational, open-label, post-marketing analysis. It included all patients who received IA hip injections. Data were sourced from hospital records and analyzed using both descriptive and inferential statistical methods.

Patient selection. Records of outpatients diagnosed with symptomatic hip OA, characterized primarily by pain, stiffness in the hip joint, and decreased walking ability and treated with IA injections between 2005 and 2023 were reviewed. Patients were followed through clinical visits scheduled approximately every six months. Baseline and follow-up data were systematically recorded in the Antiage registry.

Inclusion criteria for the study were: age ≥18 years, a diagnosis of symptomatic hip OA according to the American College of Rheumatology (ACR) criteria persisting for at least one year and up to 72 months of follow-up.[12]

Exclusion criteria included the concurrent use of oral anticoagulant therapy and the presence of significant comorbidities (e.g., rheumatologic diseases, chronic low back pain, femoral head osteonecrosis). In May 2023, a team of investigators, consisting of three rheumatologists and a rehabilitation physician, applied these criteria to extract eligible patient data from the registry. Baseline data included clinical history and demographic details. Radiological assessments were performed using the Kellgren-Lawrence grading system for hip OA on non-weight-bearing X-rays taken no more than six months prior to treatment.[13] Pain was quantified using a 100-mm visual analogue scale (VAS)[14] and function was evaluated by the Lequesne index.[15]

Each patient received a single IA injection of HA into the affected hip every six months. Different formulations of HA were utilized, varying in molecular weight (low or high), structural characteristics (linear or cross-linked), volumes (2 or 4 ml), and concentrations (20, 30, or 60 mg/ml). If clinically indicated, up to two additional injections were permitted, with a maximum frequency of one injection every three months, within a one-year period. Injections were administered every six months, even in patients demonstrating clinical improvement, to sustain therapeutic benefits and prevent disease flares. US guidance was employed for all IA procedures to ensure precise delivery. Follow-up assessments at six-month intervals included evaluations of pain via the 100-mm VAS and Lequesne index throughout the 72-month study period, consistent with standard clinical and therapeutic practices at our institution. Radiographic assessments were repeated every 24 months using standard X-rays. Dropouts were defined as patients lost to follow-up due to missed visits or treatment sessions, as well as those transferred to other healthcare facilities. Patients who died or underwent total hip replacement (THR) were also categorized as dropouts.

All data presented were derived from the Antiage registry and approved by the Ethical committee of Azienda Ospedaliera San Camillo Forlanini, Rome. Informed consent was obtained from all participants.

Statistical analysis

Descriptive statistics were employed to represent the characteristics of the patients and subgroups in this study, where applicable. For continuous variables, the reported measures included mean, range, and sample size, while for categorical variables, counts and proportions were presented. No tests for normality distribution of the data were conducted.

Data analysis was performed using SPSS statistical software. Changes from baseline in the Lequesne index, pain measured on the VAS, and NSAIDs usage were documented at each follow-up point and compared with baseline using paired t-tests to assess statistical significance. The alpha value was adjusted for multiple comparisons, as noted for each analysis, to account for the number of analyses performed on each variable. Odds ratios (ORs) and their respective 95% confidence intervals (CIs) were calculated, with a significance level set at $p = 0.05$, and were cross-classified across patient subgroups.

The initial classification of patients was performed to investigate gender-based differences. Additionally, the

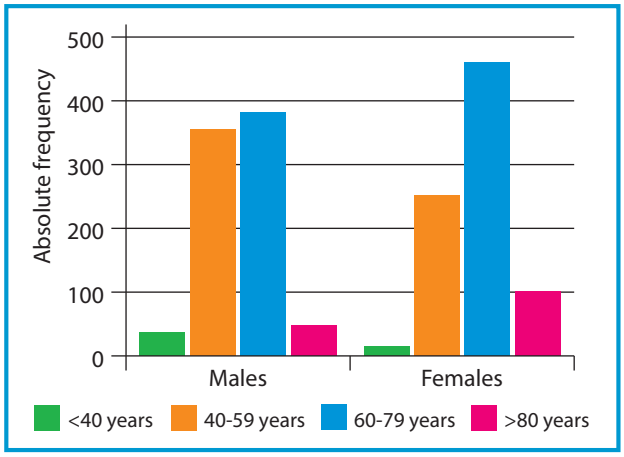

Figure 1. Age classes categorized by gender.

patient cohort (men vs women) was stratified by baseline age into the following categories: patients under 40 years (with potential OA causes including strenuous activity, sports, and overuse), patients aged 40-59 years, patients aged 60-79 years, and patients aged 80 years and older (Figure 1). Another classification involved the distribution of patients (men vs women) by BMI, categorized into normal weight, overweight, and obese groups.

Results

A total of 1,655 patients were included in this study, with a mean age of 62.5 years (range: 21-94). Assessment values were recorded at baseline and every six months for up to six years, with statistical analysis performed on the data collected at these intervals. Descriptive statistics for the study cohort are provided in Table 1. Data on pain VAS, Lequesne index, and NSAIDs consumption (days of use per month) were collected and analyzed by gender, age categories (<40, 40-59, 60-79, ≥80), and BMI classification (normal weight, overweight, obese). No side effects were reported.

Results categorized by gender

Compared to baseline, VS resulted in a statistically significant reduction in pain VAS, Lequesne index, and NSAIDs consumption ($p < 0.05$) across all groups over time (Figure 2). Summarizing all variables, a reduction was observed following the first injection and sustained throughout the six-year period. Women demonstrated higher baseline values (VAS: 6.05 vs 5.28; Lequesne index: 9.08 vs 7.15; NSAIDs consumption: 6.93 vs 4.86), which were maintained throughout the study (VAS: 4.2 vs 3.47; Lequesne index: 6.70 vs 4.79; NSAIDs consumption: 3.48 vs 1.77). There was a significant gender difference in baseline NSAIDs consumption (men: 4.86 vs women: 6.93, $p < 0.001$).

Table 1. Characteristics of the sample at baseline

Total patients (n)	1,655
Males	822 (49.7%)
Females	833 (50.3%)
Age (years, mean)	62.5 (range 21-94)
BMI (mean)	26.4 (±2.9 SD)
Weight (kg, mean)	74.01 (range 41-140)
Height (cm, mean)	168.03 (range 130-193)
Smokers	105 (6,7%)
Pain VAS mean	5.66 (2.3 SD)
Lequesne index mean	8.12 (4.42 SD)
NSAIDs intake (days/months mean)	5.9 (9.3 SD)
Concomitant knee OA	388 (23.4%)
Diabetes mellitus	70 (4.2%)
Age classes (years)	
Under 40	51 (3.1%)
40-59	606 (36.9%)
60-79	840 (51.1%)
80-99	147 (8.9%)
Hip affected*	
Right	872 (57.6%)
Left	642 (42.4%)
BMI categorization*	
Normal	590 (39.8%)
Overweight	677 (45.8%)
Obese	212 (14.4%)

* Some participants are missing data for this variable.

Results categorized by gender and age

Age class: under 40. VS led to a significant reduction in pain VAS, Lequesne index, and NSAIDs consumption ($p < 0.05$) compared to baseline in all groups (Figure 3). Men under 40 showed a greater reduction in these parameters, although this data was not adjusted for comorbidities, possibly influenced by menstrual cycle-related pain in women.

Age class: 40-59. Significant reductions in pain VAS, Lequesne index, and NSAIDs consumption were observed post-VS ($p < 0.05$) in all groups (Figure 4). Women aged 40-59 experienced greater initial reductions in VAS and Lequesne index, while men demonstrated more pronounced reductions after 72 months. Men consistently showed greater reductions in NSAIDs consumption throughout the study period. A significant baseline gender difference was noted in NSAIDs use (men: 4.98 vs women: 7.15, $p = 0.02$).

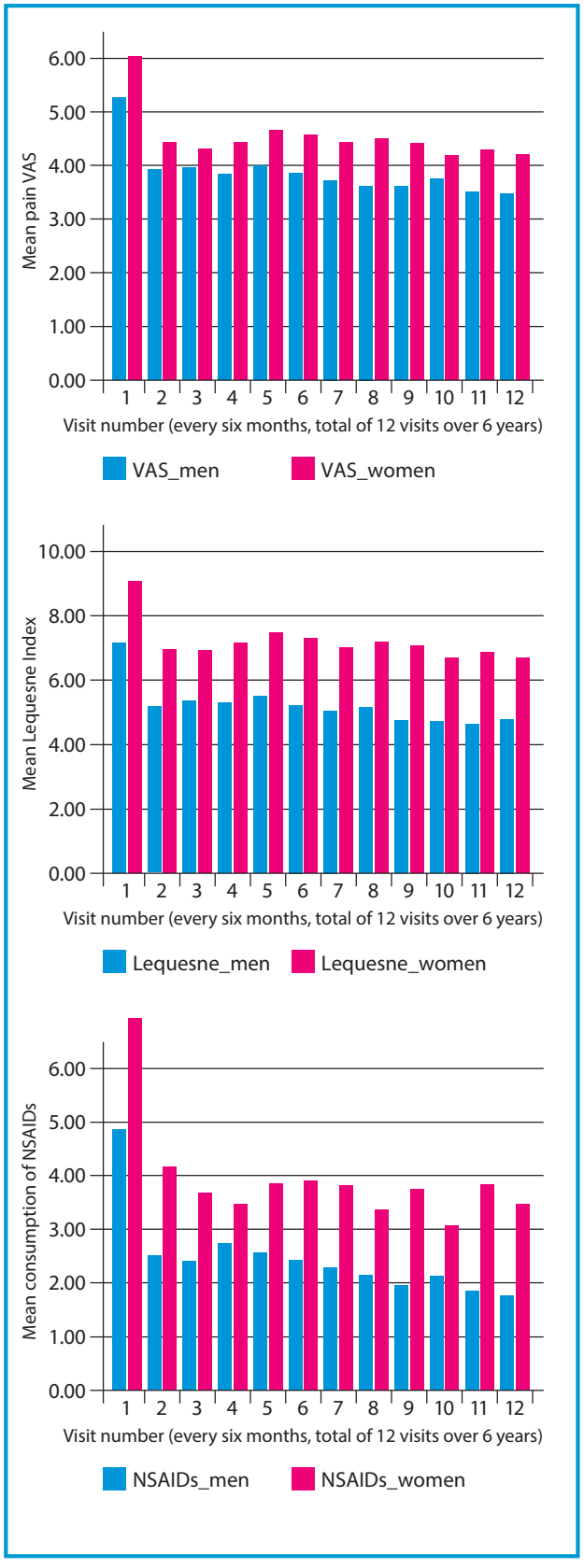

Figure 2. Results of three parameters (pain VAS, Lequesne index, consumption of NSAIDs) categorized by gender.

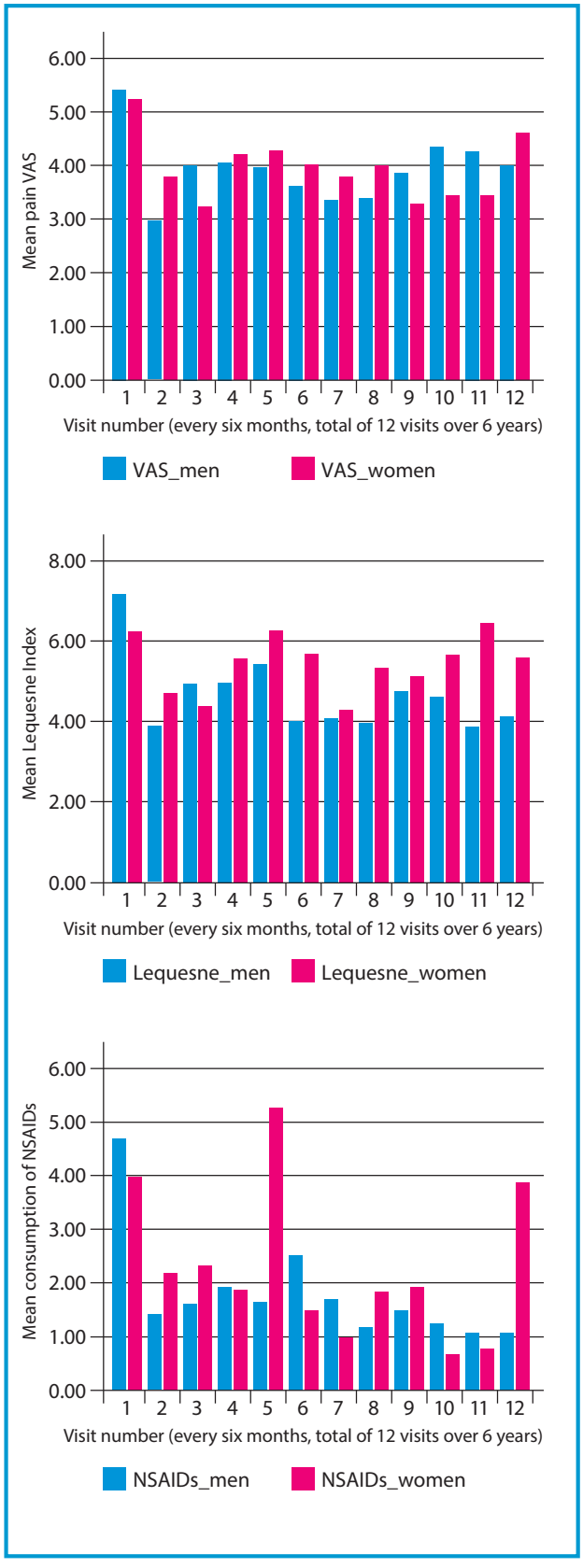

Figure 3. Results of the three parameters (pain VAS, Lequesne index, consumption of NSAIDs) categorized by gender and age (<40).

Age class: 60-79. Statistically significant reductions in pain VAS, Lequesne index, and NSAIDs consumption ($p < 0.05$) were observed over time in all groups (Figure 5). In the 60-79 age group, significant baseline gender differences were found in all parameters: pain VAS (men: 5.11 vs women: 6.07, $p = 0.045$), Lequesne index (men: 6.82 vs women: 9.2, $p = 0.002$), and NSAIDs consumption (men: 4.53 vs women: 6.86, $p < 0.001$).

Age class: ≥80. Significant reductions ($p < 0.05$) were observed over time in this group as well (Figure 6). Unlike other age groups where women had worse scores, no significant baseline gender differences were found in this subgroup.

Results categorized by BMI and gender

The study population included 590 normal-weight patients (BMI 18-25), 677 overweight patients (BMI 25-30), and 212 obese patients (BMI 30-40). All BMI groups showed significant reductions in pain VAS, Lequesne index, and NSAIDs consumption at all follow-up points compared to baseline ($p < 0.05$).

Normal weight class

Female patients exhibited higher baseline pain scores than male patients. A statistically significant reduction ($p < 0.05$) was observed at six months, continuing progressively until 72 months (Figure 7). The Lequesne index showed a similar trend with no notable gender differences, with reductions starting at six months ($p < 0.05$) and continuing up to 72 months. Significant gender differences in NSAIDs consumption at baseline were noted (men: 4.06 vs women: 6.39, $p < 0.001$). Similar to pain VAS and Lequesne index, NSAIDs consumption showed a reduction at six months, maintained through 72 months.

Overweight class

The 677 patients in this group exhibited a rapid decrease in clinical indices after the first injection, which was sustained over 72 months (Figure 8). A significant baseline gender difference was noted in NSAIDs consumption (men: 4.96 vs women: 7.42, $p < 0.001$).

Obese class

The obese subgroup included 212 patients. Statistically significant reductions in all parameters were noted at six months ($p < 0.05$), sustained up to 72 months (Figure 9). Obese women appeared to show a greater reduction in pain VAS compared to men. Baseline gender differences in NSAIDs consumption were also significant (men: 5.67 vs women: 7.62, $p = 0.006$).

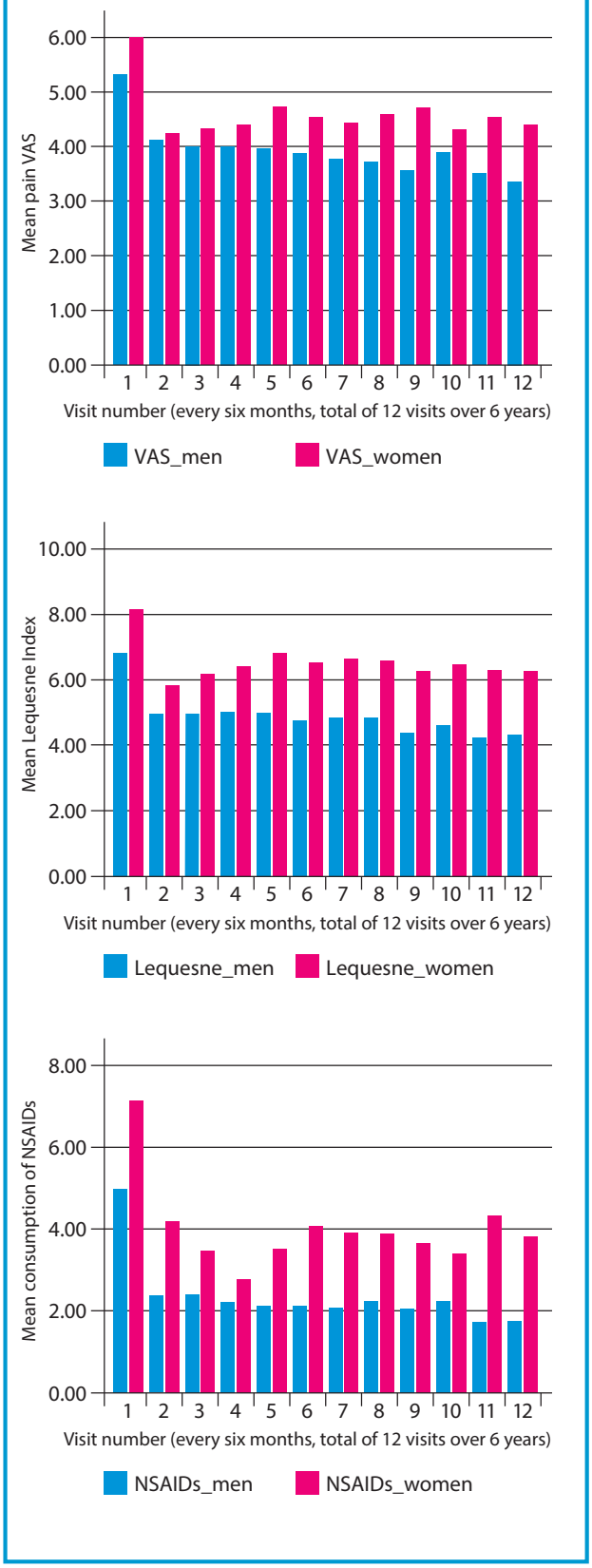

Figure 4. Results of the three parameters (pain VAS, Lequesne index, consumption of NSAIDs) categorized by gender and age (40-59).

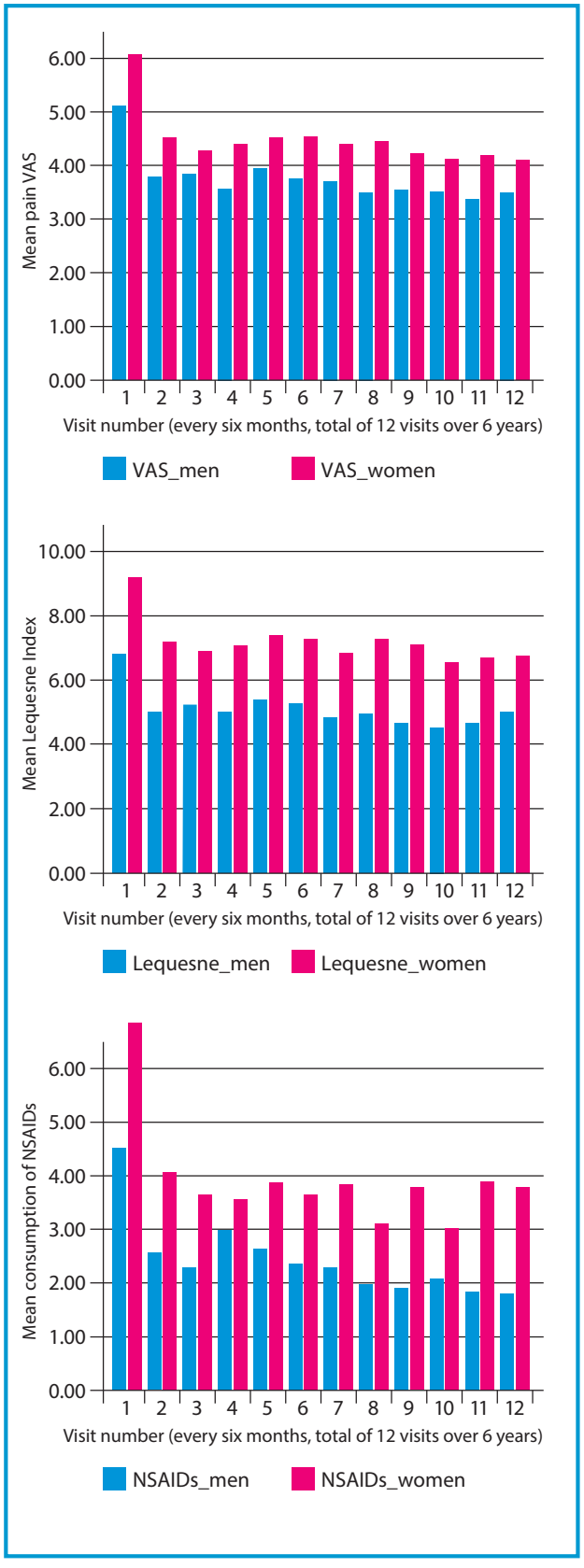

Figure 5. Results of the three parameters (pain VAS, Lequesne index, consumption of NSAIDs) categorized by gender and age (60-79).

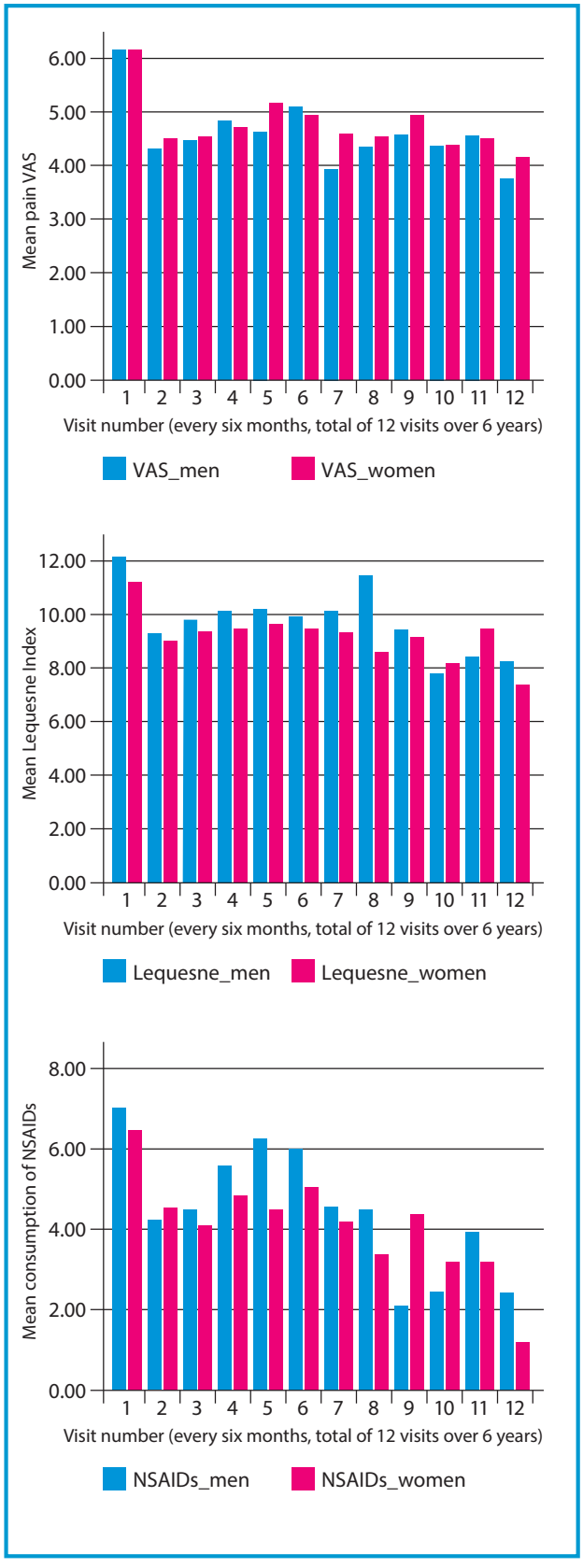

Figure 6. Results of the three parameters (pain VAS, Lequesne index, consumption of NSAIDs) categorized by gender and age (≥80)

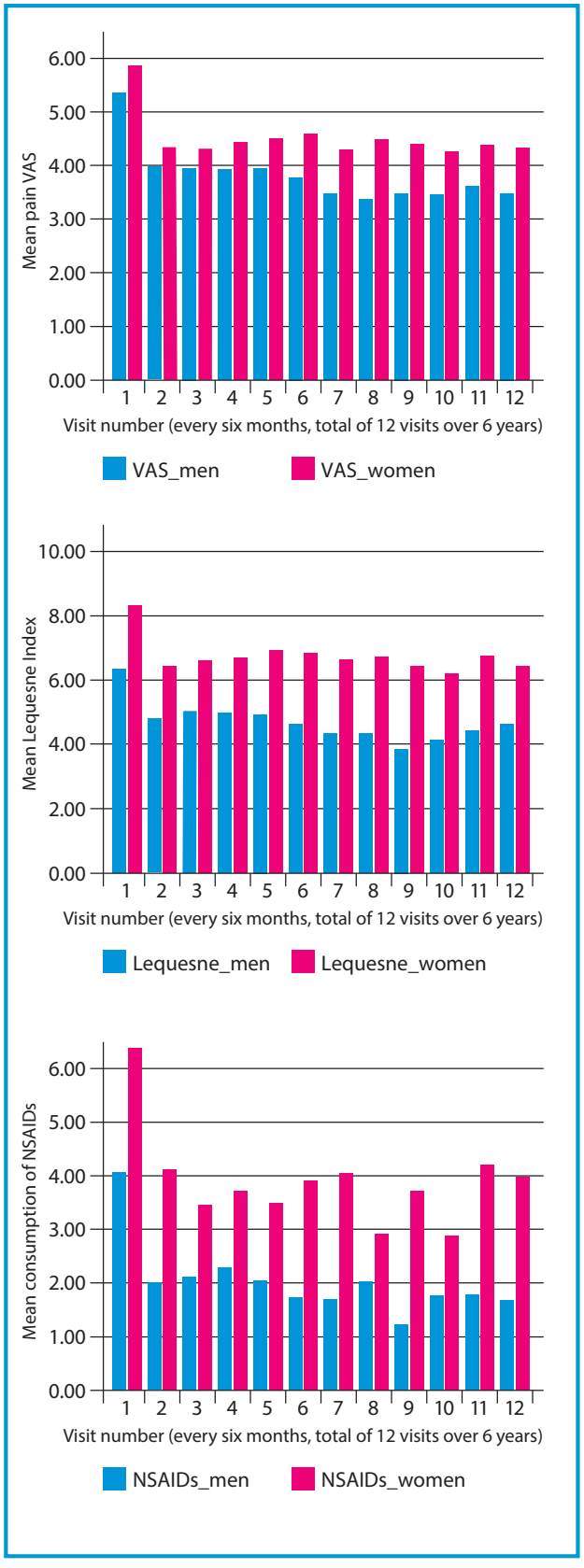

Figure 7. Results of the three parameters (pain VAS, Lequesne index, consumption of NSAIDs) categorized by gender and BMI (<25).

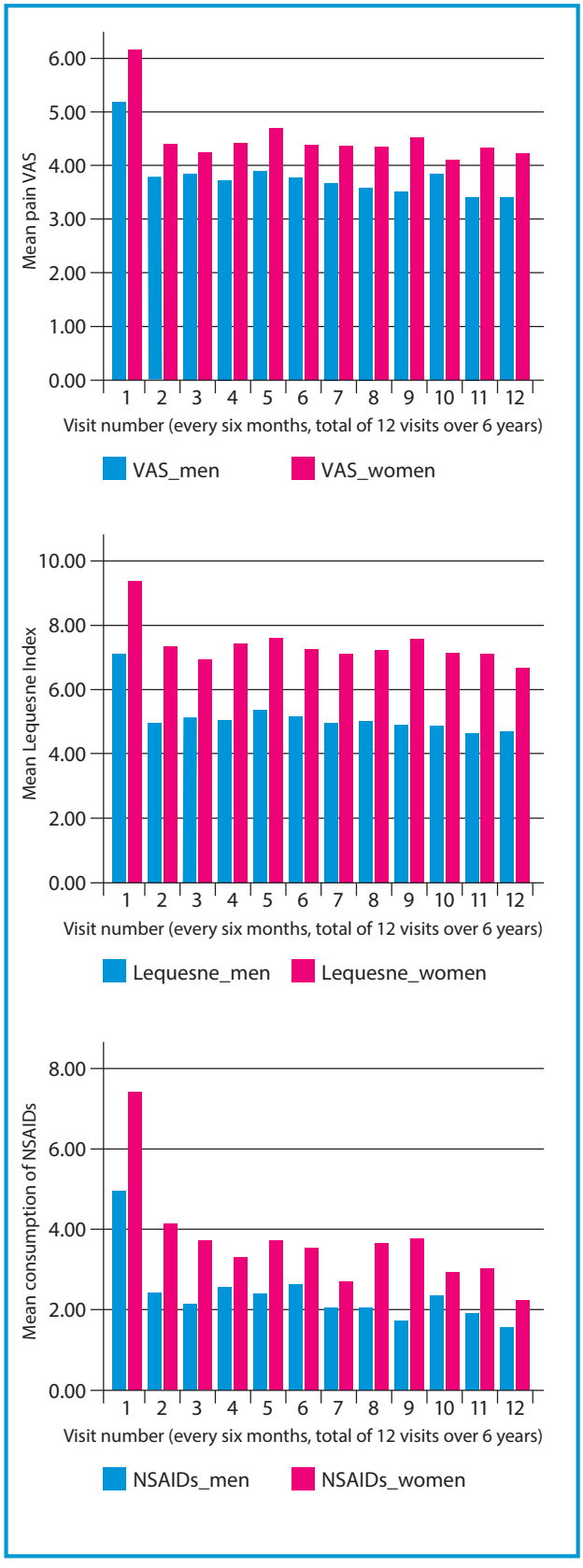

Figure 8. Results of the three parameters (pain VAS, Lequesne index, consumption of NSAIDs) categorized by gender and BMI (25-30)

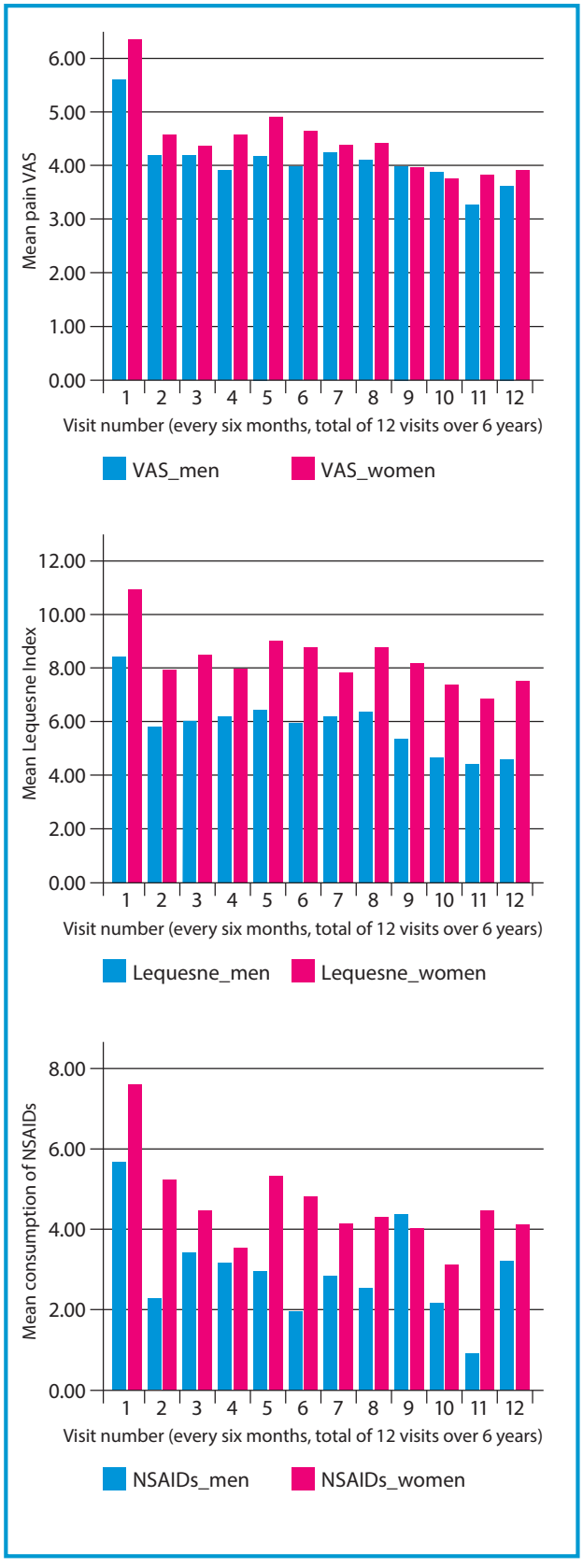

Figure 9. Results of the three parameters (pain VAS, Lequesne index, consumption of NSAIDs) categorized by gender and BMI (>30)

Discussion

To our knowledge, this is the first study to evaluate the efficacy and safety of VS with HA in a large cohort of hip OA patients over an extended follow-up period of six years. This observational study corroborates previous findings on VS efficacy and safety, demonstrating that its effects are sustained over time even with repeated injection cycles (Table 2). US-guided HA injections administered biannually appear to provide an effective dosage regimen for symptoms control, with the US guidance technique proving essential to injection accuracy and subsequent treatment effectiveness.[16] These data support VS as background therapy in hip OA, together with other pharmacological and non-pharmacological interventions. Notably, VS achieved consistent symptoms reduction across both genders, suggesting that it can effectively manage OA in real-world settings. Our results indicate that factors such as gender, age, and BMI categories may influence individual patient responses to VS, allowing for a better understanding of who may benefit most from this treatment.

A statistically significant reduction in pain VAS, Lequesne index, and NSAIDs use was observed at every time point from the first treatment onward. Our cohort's age distribution aligns with typical OA demographics, peaking between ages 50-70. However, the study also included younger patients (33 men and 18 women under age 40), likely due to sports and work-related activities, as well as a substantial group of 756 patients over age 60, demonstrating VS's utility in both younger and older populations.

Our analysis revealed several gender and age-related differences. Overall, men experienced greater reductions in pain, functionality (as measured by the Lequesne index), and NSAIDs consumption, with the latter decreasing by 53.58% after six years. At baseline, male patients under 40 reported higher pain scores than their female counterparts, whereas women had higher baseline values in older age groups. In the 40-59 age group, women showed greater initial improvements in pain (-29.33% vs -22.51%) and functionality (-28.25% vs -26.98%) compared to men. Conversely, no significant gender difference was observed in patients over 80, potentially due to hormonal changes or similar pain sensitivities in both genders, though further studies are needed to confirm this. Within the 60-79 age group, sub-analysis revealed that gender differences persisted until age 80, further highlighting the unique dynamics in OA response by age.

Baseline NSAIDs consumption showed statistically significant gender differences in normal-weight patients (men 4.06 vs women 6.39, $p < 0.001$). Both normal-weight men and women exhibited similar trends in pain and functionality improvement. This gender disparity in NSAIDs use was also noted in overweight and obese groups, though without significant differences in pain VAS or Lequesne index scores.

Table 2. Summary of the main results

General population	■ A reduction after the first injection, maintained over time for up to 6 years for all outcomes ■ In women, higher values at baseline, maintained over time for up to 6 years ■ A statistically significant gender difference at baseline regarding NSAIDs consumption (males 4.86 vs females 6.93, p <0.001)
Class age <40	■ A reduction after the first injection, maintained over time for up to 6 years for all outcomes ■ In men, a larger reduction in pain VAS, Lequesne index and NSAIDs consumption ■ No gender difference at baseline
Class age 40-59	■ A reduction after the first injection, maintained over time for up to 6 years for all outcomes ■ Women showed a greater reduction in VAS and Lequesne at the beginning ■ Men showed a greater reduction after 72 months ■ Men had a greater reduction in NSAIDs consumption at all times
Class age 60-79	■ A reduction after the first injection, maintained over time for up to 6 years for all outcomes ■ Statistically significant gender difference at baseline about all 3 parameters, with higher values in women
Class age ≥80	■ A reduction after the first injection, maintained over time for up to 6 years for all outcomes ■ No gender difference in the baseline values of VAS, Lequesne and NSAIDs consumption
BMI <25	■ A reduction after the first injection, maintained over time for up to 6 years for all outcomes ■ A statistically significant gender differences in normal weight patients at baseline about consumption of NSAIDs
BMI 25-30	■ A reduction after the first injection, maintained over time for up to 6 years for all outcomes ■ A statistically significant gender differences in normal weight patients at baseline about consumption of NSAIDs
BMI >30	■ A reduction after the first injection, maintained over time for up to 6 years for all outcomes ■ A statistically significant gender differences in normal weight patients at baseline about consumption of NSAIDs

At baseline, obese patients reported the highest pain scores and Lequesne index values, yet they showed significant improvement after the first injection, with sustained benefits over time. Overweight patients had slightly lower baseline values but showed similar positive trends. Notably, overweight women achieved the greatest pain reduction (VAS -28.73%), while overweight men showed the greatest functional improvement (Lequesne -29.72%).

The literature on intra-articular steroid injections for hip osteoarthritis and gender-related outcomes is mixed. Deshmukh et al. (2011) found that gender did not predict the efficacy of steroid injections, although radiographic severity did.[17] Perruch suggested men experienced longer-lasting relief compared to women,[18] while other studies did not report gender-related efficacy differences for VS.[19,20] For PRP a review of 30 RCTs found no significant gender differences[7], although one RCT indicated women achieved greater pain reduction than men.[8]

There are some limitations in this study. This is not a prospective study and confounding factors such as diabetes, smoking status, vitamin D levels and physical or work activity were not evaluated. These factors may influence response to VS. Additionally, data on comorbidities, treatments, OA severity in other joints and symptomatic slow-acting drug for osteoarthritis (SYSADOA) use were not collected. Despite these limitations, the large sample size and extended follow-up period provide valuable insights. Future research should analyze the effects of individual HA products, as this study considers VS as a single treatment category.

Conclusions

Future research should consider OA patient subpopulations, including phenotypes and gender differences, when assessing the effectiveness of HA treatments. Current literature offers limited data on gender disparities in the use of VS for OA, and this study provides valuable evidence to guide future clinical applications.

Our findings show that VS is effective in both men and women, with comparable effect sizes across genders. While women exhibited higher baseline values across all subsets, their treatment outcomes were similar to those of men. Interestingly, in patients over 80 years of age, baseline gender differences appeared to diminish. These results underscore the importance of continued research to optimize HA treatment strategies and improve patient care.

Abbrevations VS: viscosupplementation; OA: osteoarthritis; HA: hyaluronic acid; US: ultrasound; VAS: visual analogic scale; NSAIDs: non-steroidal anti-inflammatory drugs; BMI: body mass index; ROA: radiographic knee osteoarthritis; KOA: knee osteoarthritis; TKR: total knee replacement; KSS: Knee society score; SF: short form; PRP: platelet-rich plasma; YLD: years of healthy life lost due to disability; PROMs: patient-reported outcome measures; ACR: American College of Rheumatology; CI: confidence intervals; RCT: randomized controlled trial; SYSADOAs: symptomatic slow-acting drug for osteoarthritis.

Key messages

- Viscosupplementation is a valid treatment option for managing hip osteoarthritis.
- There is a limited number of studies examining gender differences in treatment responses among patients with hip osteoarthritis.
- The literature presents conflicting results regarding treatment outcomes in terms of pain relief, functional improvement, and NSAIDs use.

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Ethical approval and informed consent. All the data provided are based on the Antiage register and were obtained with the approval of the Ethical Committee of Azienda Ospedaliera San Camillo Forlanini, Rome. Research was conducted in accordance with the WMA Helsinki Declaration. The informed consent statement was obtained from all individuals to administrate HA injection e to authorize the use of their data.

Authors' contribution statement. Migliore A. and Amato P. conceived of the presented idea. All authors participated in conceiving the content. Migliore A. and Iannarelli N. developed the methodology. Iannarelli N., Saporito R. and Maggiolini F. performed the computations. Iannarelli N. performed the statistical analysis. Massafra U. and Giovannangeli F. performed a narrative review of the literature about gender difference in OA. De Vito A. and Saccone L. supervised the findings of this work. All authors discussed the results and contributed to the final manuscript. Migliore A. and Iannarelli N. wrote the manuscript with support from the other authors. All authors participated to perform the final review.

Conflicts of interest statement. All authors declare no conflicts of interest.

Correspondence to:
Nazzareno Iannarelli
Department of Medical and Surgical Specialties
University of Campania "Luigi Vanvitelli"
Piazza Luigi Miraglia 2
80138 Naples, Italy
Email i.nazzareno@gmail.com