Sexual dimorphism in patellofemoral pain syndrome: Biomechanical differences and biological influences

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Biomechanical and Biological Factors of Sexual Dimorphism in Anterior Knee Pain: Current Concepts

Abstract

Female gender is one of the commonly mentioned risk factors for anterior knee pain (AKP), among a spectrum of other factors including anatomical, biomechanical, hormonal, behavioral, and psychological elements contributing to its development. Despite the focus on individual risk factors, there's a notable gap in comprehending how gender influences and interacts with other risk factors. The objective of this review was to identify and emphasize the connections between these interactions, gender-related risk factors for AKP, and the potential mechanisms that explain their associations with other risk factors, aiming to aid in the creation of precise prevention and treatment approaches. Gender influences the majority of risk factors for AKP, including anatomical, biomechanical, hormonal, behavioral, and psychological factors. Women have on average smaller patellae, higher patellofemoral cartilage stress and for AKP, disadvantageous trochlear morphology, ligament and muscle composition and unfavorable neuromuscular control pattern. In contrast, men show on average an increased ability to strengthen their hip external rotators, which are both protective against AKP. Particularly in kinetic and kinematic analysis, men have been shown to have a distinctly different risk factor profile than women. Sex hormones may also play a role in the risk of AKP, with estrogen potentially influencing ligamentous laxity, increasing midfoot loading and affecting neuromuscular control of the lower extremities and testosterone positively affecting muscle mass and strength. The higher incidence of AKP in women is likely due to a combination of slightly increased risk factors. Although all risk factors can be present in both men and women and the holistic evaluation of each individual's risk factor composition is imperative regardless of gender, knowing distinctive risk factors may help with focused evaluation, treatment, and implementing preventive measures of AKP.

Text Boxes:

Current concepts:
- Differential emphasis should be put on strengthening exercises based on gender-specific muscle weaknesses: Females benefit more from a hip/core and knee strengthening rehabilitation program than men, but show less capability to strengthen muscles.
Particularly in active women experiencing anterior knee pain, it's important to examine the vastus medialis : vastus lateralis ratio and vastus medialis muscle delay, and consider interventions focused on neuromuscular control.

In women specifically, pain-related disability is influential, emphasizing the need to target a comprehensive pain solution.

Tailored recommendations should consider gender differences, including education on the impact of high heels, for modifying activities or managing loads.

**Future perspectives:**

- **Advanced Biomechanical Studies:** Exploring nuanced differences in joint kinetics and muscle activation patterns between genders for a deeper understanding of anterior knee pain variations.

- **Hormonal Influence:** Delving into the impact of hormonal variations across the menstrual cycle or hormonal therapies on anterior knee pain, shedding light on potential interventions.

- **Longitudinal Studies:** Conducting long-term studies tracking the progression and prevalence of anterior knee pain in both sexes to identify potential predictors and preventive measures.

- **Technology Integration:** Leveraging advancements in wearable technology and imaging techniques to track biomechanical changes and assess treatment effectiveness in men and women with anterior knee pain.
Introduction

One of the most commonly cited risk factors for anterior knee pain (AKP) is female gender[1], with females having double the risk of developing AKP than men[2]. Among females aged 18-35 years, the prevalence of AKP is reported to range between 12-13%[3], constituting an important portion of the population. Anterior knee pain ranks among the most prevalent knee disorders in sports medicine clinics, constituting approximately 25% of all knee injuries[4]. The development of AKP is multifactorial, including various elements such as structural malalignment, altered biomechanics and dynamic movement pattern variances[1]. While gender and mechanical risk factors are commonly seen as separate elements, gender actually has an impact on various other risk factors (figure 1). Understanding the role of gender in AKP carries profound clinical implications as acknowledging gender disparities in AKP is essential for healthcare professionals to address the specific needs of the affected population. By unraveling the nuanced interplay between gender and other risk factors clinicians can devise more targeted and effective interventions. Moreover, identifying genders’ influence on AKP can identify broader aspects of musculoskeletal health and gender equity. By examining how biological, societal and cultural factors intersect to shape AKP risk, researchers can inform broader discussions on gender equity in healthcare and advocate for more comprehensive approaches to musculoskeletal health. Accordingly, this review aims to unravel the influencing components of gender on specific risk factors for AKP, with the ultimate goal of developing targeted prevention and treatment strategies that possess adaptability.

Figure 1: Interplay of gender-influenced risk factors for patellofemoral pain
Legend: This figure demonstrates the differential impact of gender on various risk factors contributing to anterior knee pain. It showcases how gender is not mainly a risk factor itself, but influences various factors that predispose men and women to this condition.

VM:VL ratio = vastus medialis : vastus lateralis ratio
Anatomical and biomechanical distinctions

Quadriceps Force Vector

The position of the patella is influenced throughout knee flexion by the forces of the quadriceps muscle. This force vector is referred to as the Q-angle, running from the patella to the anterior superior iliac spine (ASIS) and tibial tubercle.[5] A higher Q-angle may contribute to patellar maltracking and AKP.[4]. Women tend to have a wider pelvis than men[6], due to the differential selection pressure of childbearing. Although this can lead to a relative lateralization of the ASIS in the wider pelvis in women, an effect on the Q-angle could not be confirmed when correcting for height[7]. Reasons therefore could be the relative long distance between the pelvis and patella, compared to the distance between patella to the tibial tuberosity; necessitating a larger ASIS lateralization in order to affect the Q-angle. Grelsamer et al. showed in their analysis of 69 subjects an average Q-angle difference of only 2.4° between men and women, and similar values when correcting height[7]. Height was associated with the Q-angle, as the Q-angle decreased by 0.2° per centimeter height. With women being on average about 10cm shorter than men, this factor may have more influence on the Q-angle than the pelvic width itself. Other authors have reported higher variations between men and women (women 2.5 – 10° vs men 0 - 8°), and female AKP patients show higher maximum Q-angles than their male counterparts[8]. Another knee-focused assessment method to estimate the force vector of the quadriceps muscle in relation to the trochlea is the tibial tubercle-trochlear groove (TT-TG) distance. Carlson et al. showed slightly higher TT-TG distances in men with and without AKP than in women (AKP women 12.9mm vs men 13.2mm; healthy controls women 10.5mm vs men 12.0mm), but this gender difference was not significant[9]. This result was confirmed by Li et al., who found a slight, but significant average 1.4mm larger TT-TG in men than in women[10]. These intergender variations were only subtle and within normal thresholds (normal TT-TG 11 ± 2.5 mm) in both patients with and without AKP[10].
Hip positioning

In addition to directly affecting patellar movement, the force vector of the quadriceps can also affect the position of the femur. This is especially relevant in patients with weak hip girdle musculature. Although retrospective cohort studies have hypothesized hip weakness as a risk factor for AKP, prospective studies could not show a direct relationship between hip weakness (neither isometric strength of hip abduction, adduction, extension, flexion, external rotation, nor internal rotation) and AKP[11]. Both larger Q-angles and weak hip musculature are associated with greater hip adduction and internal femoral rotation[12], resulting in dynamic knee valgus. Females with and without AKP demonstrate greater peak knee valgus than men[13]. Yang et al. investigated the kinematics of recreational runners during running and compared AKP groups with controls and pain conditions (AKP group with active knee pain and without knee pain during testing) and compared sexes[14]. Both females and males with AKP had increased peak knee valgus while running without pain compared to matched controls. Interestingly, males with AKP also had an increased peak knee flexion angle when running without pain compared to controls, which did not decrease when running with pain. In their prospective cohort study involving 4543 participants, Boling and colleagues investigated whether males and females exhibit distinct kinematic risk factor profiles for AKP. Their findings led to the conclusion that indeed, males and females have varying risk factor profiles for AKP development[15]. Females with AKP presented with less than 10° of hip abduction at initial contact and greater than 10° of knee internal rotation at 50% of the stance phase. In contrast, males with greater than 20° of knee flexion at initial contact and between 0 and 5° of hip external rotation at 50% of the stance phase showed a decreased risk of developing AKP.

Patellofemoral joint anatomy

Another gender related anatomical risk factor for AKP can be a differing anatomy of the patellofemoral joint itself. Human knee joints exhibit gender-specific disparities in articular cartilage volume, thickness, surface area and cartilage stress: Females tend to have smaller patellae, with less patellar and trochlear cartilage thickness (22% less patella- and 23% less femur- cartilage thickness in females[16]), cartilage volume (average patella cartilage volume female 2.97ml vs male 3.56ml)[17] and a 23% smaller joint contact area[18]. Besier et al. showed that females manifest greater cartilage stress compared to males (female 2.2 J/m³ vs male 1.3 J/m³) and show higher quadriceps muscle forces compared to their body weight (female 3.7x body weight vs male 3.3x bodyweight)[18]. Draper et al. investigated differences in the load-bearing patellofemoral joint cartilage between genders in 34 patients with patellofemoral pain and 16 healthy controls and concluded that a thin patellar cartilage may
contribute to AKP in males, but in their cohort did not to contribute to AKP in females[16].

Additionally, trochlear groove anatomy varies between the sexes. In an anatomical study using 3D reconstructions of CT scans, females were found to have wider and shallower trochlear grooves compared to their male counterparts[19]. Orientation of the trochlear groove may also differ between the sexes, with females tending to have a more medially oriented proximal trochlear groove[20]. All of this may contribute to the higher prevalence of AKP in more likely women.

Muscle strength

The quadriceps muscle group contributes to dynamic patellar stabilization and knee joint mechanics. Relative weakness of the quadriceps muscle can lead to increased stress on the osteochondral patella[21] and potentially contribute to the development of AKP, but it is unclear whether decreased quadriceps strength is a cause or a consequence of anterior knee pain, or a result of both. Barton et al. summarized in their systematic review that individuals with AKP had weaker quadriceps muscles compared to those without knee pain, but did not specifically investigate differences in quadriceps strength between men and women[22].

Bolgla et al. investigated therapy results of 185 patients with patellofemoral pain and showed that after a six-week hip/core or knee strengthening rehabilitation program 88 females (71%) reported improvements in pain and patient-reported function, whereas only 36 males (59%) reported improvements[23]. The authors could not confirm that either gender would respond more favorably to the hip- or knee-focused program, but found different patterns of strength gains between males and females who responded favorably or unfavorably. For example, male responders showed an 8% lower baseline value of hip external rotator strength than non-responders, which then increased by 15.4%, but female responders only had a modest 5% increase in hip external rotator strength. Both sexes showed comparable improvements in hip extensor strength. This finding suggests that females may have less ability to strengthen their external hip rotators. Consequently, if muscle weakness is present in women or men, interventions aimed at enhancing the hip external rotators may be more advantageous for males than females.

Core musculature also plays a role in providing a stable base for generating or resisting forces in order to maintain balance and control the distribution of vertical ground reaction forces. Botta et al. compared trunk muscle endurance among females and males with (n=148) and without AKP (n=92)[24]. Females with AKP had decreased anterior and lateral trunk muscle endurance compared to their sex-matched controls, but this finding was not found in the male groups. Other studies showed such similar results that females with AKP seem to
have impaired trunk muscle function[25], which may be due to a larger muscle cross-sectional area reported in men[26] or training preferences. This highlights the importance of trunk muscle endurance, especially in females with AKP.

Muscle activation patterns

Muscle activation patterns also may play a substantial role in reducing the incidence of anterior knee pain. Delayed vastus medialis activation in comparison with the vastus lateralis was associated with AKP in multiple studies[27]. There is some evidence to suggest that the vastus medialis: vastus lateralis (VM:VL) ratio may differ between men and women with AKP. Earl et al. found that women with AKP had a lower VM:VL ratio compared to healthy women, but there were no significant differences in VM:VL ratio between men with AKP and healthy men[28]. Pal et al. showed that this finding is dependent on whether these patients are patellofemoral maltrackers with both abnormal tilt and abnormal bisect offset [29]. Also, a correlation between patellar tilt and VM:VL activation ratio is only found in AKP patients with a maltracking patella[30]. Briani et al. investigated if the level of activity of women influenced this delayed vastus medialis activation pattern and found that women who had a high level of activity had the largest VMO delay while women with moderate activity levels did not have a delay compared to a control group[31]. Although the reason for these differences in neuromuscular control patterns between the sexes remains unknown, the discovery that these patterns are more prevalent in active women may have implications for targeted treatment.

Hormonal distinctions

Traditionally in sports medicine, sex hormones are often thought of in the context of energy deficiencies, bone health, stress fractures, and menstrual cycle perturbations in athletes. Recently, this interest has expanded to investigate if hormone level variations lead to corresponding injury risk fluctuations[32]. High estrogen levels have been associated with mechanical ligament weakness and women show higher a prevalence of general and local hypermobility as assessed with the Beighton score, Sachse scale or the Hakim & Grahame questionnaire[33; 34]. Athletes with generalized joint laxity show increased midfoot loading[35], which is associated with patellofemoral pain in runners[36]. Local hypermobility due to hormonal influences of estrogen were initially examined in the anterior cruciate ligament (ACL) literature, where the average ACL laxity seems to increase in the ovulatory phase of the menstrual cycle. Studies on the influence of hormones on medial patellofemoral or patellotibial ligament laxity in regards to either patellofemoral instability or patellofemoral pain are currently lacking. Although estrogen can potentially also make the patella stabilizing ligaments more lax
and thus more prone to maltracking, injury, or pain, no study has investigated this particular topic.

Nevertheless, the effects of testosterone, estrogen and progesterone go beyond mechanical properties, and also affect cognitive, emotional and behavioral functions[37]. When performing demanding tasks as cutting and changing directions[38], vertical stop-jump tasks[39], and jump landing[40], female subjects exhibit different patterns of electromyographic activity in their hip and lower extremity muscles compared to male counterparts. The electromyography (EMG) activity of the vastus medialis and vastus lateralis muscles during toe rise and heel rock tasks in women with AKP was examined by Samani et al. across various menstrual cycle phases[41]. The amplitude ratio of VM:VL was significantly higher in the ovulatory phase compared to the follicular phase. Cesar and colleagues observed a decreased knee joint valgus angle during the luteal phase[42]. No significant correlation was found between the onset timing of gluteus medius electromyography and knee valgus angle, suggesting that progesterone does not have a meaningful influence on gluteus medius activation during such tasks. The clinical relevance and therapeutic consequences of these neuromuscular influences have not yet been investigated, but can help with the understanding patients with this specific risk factor may feel some relief of their symptoms during the ovulatory and follicular phase. No studies have explored the effects of hormonal birth control on these findings as of yet. Targeted neuromuscular coordination treatment may be particularly important in women in all phases of the menstrual cycle and should be considered.

Testosterone also regulates bone and muscle mass, which could indirectly impact AKP. Low testosterone levels have been linked to decreased muscle mass and strength[43], which could potentially increase the risk of developing AKP. Women have a smaller cross-sectional area and lower tensile strength of the quadriceps muscles than men, which may result in decreased knee joint stability and increased patellar stress during weight-bearing activities. Additionally, testosterone has been shown to have anti-inflammatory properties[44], which could potentially reduce inflammation and pain in individuals with AKP. Testosterone also can affect behavior in both men and women. It has been linked to risk-taking[45], with men choosing more risk-taking contact recreational sports activities which result in a relatively higher incidence of post-traumatic injuries compared to women. Female athletes, on the other hand, tend to engage in more endurance-based activities, such as running. This results in the greater prevalence of repetitive overuse injuries in the female population. These hormonal and cultural differences at a population level are a factor in the incidence of AKP.

Psychological distinctions
Anterior knee pain has long been discussed as pure nociceptive pain, but psychological factors and pain threshold as well as hyperalgesia have been more recently investigated[46]. There is evidence to suggest that pain perception may differ between men and women and this applies also to AKP. Some studies have reported that women experience greater pain intensity and pain-related disability compared to men with this condition[1]. Psychological, psychosocial and negative mood have been shown in women to have a stronger relationship to functional impairment[47] and may magnify AKP in greater extent in women than in men. Maclachlan conducted a systematic review of non-mechanical features of patellofemoral pain and found that anxiety, depression, catastrophizing and fear of movement were correlated with pain and reduced physical function[48]. In the limited studies included, the authors could not say if these psychological disorders were result or cause of the pain, but underline the necessity of a multimodal therapy, which may be more imperative for a successful treatment in women than in men.

Cultural distinctions
Cultural and societal influences contribute to shaping the female identity within a population. One manifestation of this is the widespread use of high-heeled shoes, which holds considerable value in defining heteronormative female gender identity for many women. While high heels may offer psychosexual advantages, they can adversely affect health including changes in kinetic and kinematic alterations. Peak patellofemoral joint stress is increased with increasing heel height (low heel: 1.9±0.7 MPa, medium heel: 2.6±1.2 MPa, and high heel: 3.6±1.5 MPa)[49], which is mainly driven by higher knee extension moments which can be twice as high[50; 51]. The subgroups of the quadriceps muscle are thereby affected unequally. The research of Batista et al. revealed that wearing high-heeled shoes amplifies the activity of the vastus lateralis in comparison to the vastus medialis, exacerbating muscle imbalances commonly observed in individuals experiencing anterior knee pain[52]. Clinical implications emphasize the necessity of screening patients with anterior knee pain for high-heeled shoe usage, highlighting the importance of informing them about the potential influence of such footwear on their condition.

Discussion
In females, ligament laxity[33; 34], quadriceps strength[23], and neuromuscular control patterns[28] are crucial clinical findings to assess in the context of AKP. Ligament laxity can predispose females to AKP by compromising knee stability[33; 34]. Weak quadriceps muscles[23] and altered neuromuscular control[28] patterns may further exacerbate AKP by...
affecting patellar tracking and joint stability. The higher incidence of AKP in women is likely multifactorial, resulting from a combination of these increased risk factors. In males, additional considerations for potential differences in muscle mass and biomechanics are warranted, making rehabilitation especially important due to their typically better ability for muscle strengthening[23]. The in general greater muscle mass and different lower limb biomechanics compared to females can influence the distribution of forces across the knee joint and contribute to AKP development. Interestingly, if males do display these predisposing factors, it could theoretically be easier to treat AKP owing to their typically better capacity for muscle strengthening[23]. However, it’s essential to recognize that they might face a more substantial deficit compared to females. Tailored therapy addressing these gender-specific nuances is vital for optimizing treatment outcomes in both male and female patients with AKP. Additionally, individualized treatment plans should consider gender-specific differences in muscle mass and biomechanics to effectively manage AKP in both populations.
Table 1: Summary of gender specific risk factors for anterior knee pain

<table>
<thead>
<tr>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomical distinctions</strong></td>
<td></td>
</tr>
<tr>
<td>- Higher Q-angles due to smaller body height</td>
<td>- Lower Q-angles due to increased body height</td>
</tr>
<tr>
<td>- Smaller patellae</td>
<td>- Bigger patellae</td>
</tr>
<tr>
<td>- Higher patellofemoral cartilage stress</td>
<td>- Lower patellofemoral cartilage stress</td>
</tr>
<tr>
<td>- Lower volume of articular knee cartilage</td>
<td>- Higher volume of articular knee cartilage</td>
</tr>
<tr>
<td>- Shallow and wider trochleae</td>
<td>- Deeper trochleae</td>
</tr>
<tr>
<td><strong>Biomechanical distinctions</strong></td>
<td></td>
</tr>
<tr>
<td>- Greater dynamic knee valgus (greater hip adduction and internal femoral rotation)</td>
<td>- Dynamic knee valgus, quadriceps muscle strength and VM:VL ratio have <em>not</em> been identified as risk factors in men</td>
</tr>
<tr>
<td>- Less ability to train hip external rotators</td>
<td>- Higher ability to strengthen hip external rotators</td>
</tr>
<tr>
<td>- Weaker quadriceps muscle</td>
<td>- Stronger quadriceps muscle</td>
</tr>
<tr>
<td>- Less lower anterior and lateral trunk muscle endurance</td>
<td>- Higher lower anterior and lateral trunk muscle endurance</td>
</tr>
<tr>
<td>- Lower VM:VL ratio</td>
<td>- Higher VM:VL ratio</td>
</tr>
<tr>
<td>- Increased midfoot loading due to ligament laxity</td>
<td>- Increased peak knee flexion angle</td>
</tr>
<tr>
<td><strong>Hormonal distinctions</strong></td>
<td></td>
</tr>
<tr>
<td>- Female sex hormones increase ligament laxity</td>
<td>- Male sex hormones make participation in high risk sports more likely (posttraumatic injuries)</td>
</tr>
<tr>
<td>- Female sex hormones decrease postural stability and proprioception</td>
<td></td>
</tr>
<tr>
<td><strong>Psychological distinctions</strong></td>
<td></td>
</tr>
<tr>
<td>- Psychological, psychosocial and negative mood have a stronger relationship to functional impairment in women</td>
<td></td>
</tr>
</tbody>
</table>

*Legend: VM:VL ratio = vastus medialis : vastus lateralis ratio*
Literature:


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Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Anna Bartsch reports financial support was provided by Zaeslin Foundation, Martin Allgöwer Foundation and AO Trauma Switzerland. Dr. Sherman holds committee positions for AANA, AAOS, ACLSG, AOSSM, Biologic Association, ICRS, and ISAKOS. He is on the editorial board for the Arthroscopy Journal, Cur Rev Musc Med, and VJSM. He is a course chair of ISMF and the PFF Masters Course and a member of the AO Sports Medicine Taskforce.