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Oral Contraception Use and Musculotendinous Injury in Young Female Patients: A Database Study

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ABSTRACT

RODRIGUEZ, L. A., II, Y. LIU, S. D. SOEDIRDJO, B. THAKUR, and Y. Y. DHAHER. Oral Contraception Use and Musculotendinous Injury in Young Female Patients: A Database Study. *Med. Sci. Sports Exerc.*, Vol. 56, No. 3, pp. 511–519, 2024. **Purpose:** The purpose of this study is to characterize the effect of sex and the influence of oral contraception usage on musculotendinous injury (MTI). Current literature suggests a disparity in the incidence of MTI between males and females. This may be attributed to inherent biological differences between the sexes, such as in the sex hormonal milieu. There is a lack of information associating sex hormone milieu and MTI. **Methods:** We searched the PearlDiver database (a for-fee healthcare database) for males, females taking oral contraceptives (OC), and eumenorrheic females not taking any form of hormonal contraceptives (non-OC) 18–39 yr old. The three populations were matched by age and body mass index. We queried the database for lower-extremity skeletal MTI diagnoses in these groups. **Results:** Each group contained 42,267 patients with orthopedic injuries. There were a total of 1476 (3.49%) skeletal MTI in the male group, 1078 (2.55%) in non-OC females, and 231 (0.55%) in OC females. Both the non-OC and the OC groups had a significantly smaller proportion of MTI than males ($P < 0.0001$), and therefore these groups were less likely (adjusted odds ratios, 0.72 and 0.15, respectively) to experience MTI when controlled for potential covariates. **Conclusions:** In this study, we show that females are less likely to develop MTI to total injuries, when compared with males, with OC using females being least likely followed by non-OC females. These results are consistent with other epidemiological studies; however, overall results in the literature are variable. This study adds to the emerging body of literature on sex hormone–influenced musculoskeletal injury but, more specifically, MTI, which have not been rigorously investigated. **Key Words:** ESTROGEN, ORAL CONTRACEPTION, SKELETAL MUSCLE INJURY, TENDON INJURY, MUSCLE INJURY

Extensive literature has highlighted the significant disparity in musculoskeletal injuries between males and females (1–4). Although musculotendinous injuries (MTI) are among the most common musculoskeletal injuries in sports (5–8), research on sex disparity in musculoskeletal injuries has primarily focused on anterior cruciate ligament (ACL) injuries. Females are up to eight times more likely to suffer an ACL injury than males (9,10), whereas data regarding sex disparity in MTI between males and females are more variable and may be muscle specific (e.g., quadriceps vs hamstring) (11–13).

Traditionally, anatomical and biomechanical factors have been considered the primary drivers of these differences. However, emerging evidence suggests that female hormones, particularly estrogen, may also contribute significantly to this disparity. Studies have shown that ACL injuries occur more frequently during the late follicular phase of the menstrual cycle when estrogen (E2) concentrations are highest and progesterone (P) concentrations are still low (14,15), which may be driven by E2's catabolic effect in the connective tissue (16).

By contrast, limited data exist regarding the association between MTI and sex hormones over the menstrual cycle in females. However, preliminary data show that MTI in female athletes occurs more frequently during the late follicular phase when E2 concentrations are highest and progesterone concentrations are still low (17). Similar to the ACL, skeletal muscles and tendons are also sensitive to E2. Estrogen receptors α and

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β (ER-α and ER-β) were first identified in human skeletal muscle in 2009 (18), ER-α in human connective tissue in 1996 (19), and ER-β in human tendons in 2010 (20). E2 is beneficial for muscle strength in females (21) and may be related to E2 maintaining muscle mass (22), maintaining the satellite cell pool for regeneration (23), influencing contractility via the binding of myosin heavy chains to actin through phosphorylation of the regulatory light chain (22) and protein synthesis (myofibrillar and collagen) (16). Interestingly, lower muscle stiffness has been shown to be correlated with estrogen concentrations (24–27), which may protect the muscle from injury (28). Conversely, in tendons, E2 has been shown to affect both the collagen synthesis and the mechanical properties of the tissue, showing that females with higher estrogen may have reduced tendon strength (29). The active and passive characteristics of the musculotendon unit play a critical role in responding to exercise-induced loads and safeguarding tissues from damage. However, the extent to which the opposing effects of E2 on muscle/tendon contribute to the mechanics of the musculotendon unit and its susceptibility to injury remains unknown.

According to the Centers for Disease Control and Prevention, oral contraceptives (OC) rank as the second most commonly used contraceptive method among females15–49 yr old, after female sterilization (30). Combination OC contain exogenous ethinyl estradiol (EE) and various progestins and, when taken correctly, suppress endogenous hormone production and minimize the magnitude of endogenous hormone fluctuations throughout the menstrual cycle (31). Female patients using OC offer a clinically relevant comparison group to eumenorrheic females, as they experience more stable concentrations of endogenous sex hormones (estradiol and progesterone) and are exposed to EE and progestin. Leveraging these differences in the sex hormone milieu can provide insights into the possible effects of female sex hormones on MTI development.

In summary, limited research has focused on the role of estrogen in MTI development. Understanding the influence of sex hormones, particularly E2 and P, on MTI development is crucial for elucidating the underlying mechanisms and developing targeted interventions. Comparing OC users and non-OC users can provide valuable insights into the potential effects of exogenous EE and progestin on musculotendinous tissue integrity.

In this study, we aimed to determine if sex and/or OC usage influenced the percentage of MTI (out of a comparable number of orthopedic injuries) incurred by females. We hypothesized that male and OC groups would exhibit less MTI than the non-OC group due to low and stable hormone profiles. To achieve this, we compared the percentage of MTI between males, females using OC, and females not using OC (non-OC) by searching outcomes for these groups using a healthcare database. It is important to note that our main outcome is the percentage of MTI relative to the total orthopedic injuries in each group of patients.

METHODS

PearlDiver database. The PearlDiver database (www.pearldiverinc.com, Colorado Springs, CO, USA) is a for-fee healthcare database that houses Health Insurance Portability and Affordability Act–compliant deidentified patient medical records for private-payer, Medicare and Medicaid, as well as patients receiving insurance through healthcare exchanges. It contains pertinent information on medical procedures, diagnoses, and drug prescriptions for patients. Our study used the M30Ortho dataset. The M30Ortho dataset exists within the larger PearlDiver database and pertains specifically to orthopedic injuries. At the time of our study, the M30Ortho dataset covered patient data from January 1, 2010, to December 31, 2019.

Study sample. Patient records were filtered based on the *International Classification of Diseases, 9th Revision* (ICD-9), ICD-10, and current procedural terminology (CPT) codes. All the information was deidentified and compliant with the Health Insurance Portability and Affordability Act and publicly available. Therefore, the UT Southwestern Human Research Protection Program concluded that this study did not require IRB approval or oversight. The initial patient cohorts were first selected by their specific body mass index (BMI) ranges. We focused on patients in the normal to overweight categories, which correspond to a BMI of 19 to 30.9 ($kg \cdot m^{-2}$). This was further filtered by sex and age to find patients 18 to 39 yr old and those not using hormone replacement therapy, to capture the premenopausal adult population and to exclude those patients with hormone disturbances (Fig. 1). After this first layer of filtering, groups of patients were assigned to male, non-OC users (females with no history of hormonal contraceptive use), and female OC users groups. Initially, the OC group was defined as patients who were prescribed common OC (32) (Table 1). The OC user group was further filtered for patients that were prescribed OC at least 1 yr before their injury and were still prescribed OC after the injury. We excluded all female patients who had been diagnosed with amenorrhea, oligomenorrhea, and polycystic ovary syndrome. This resulted in a non-OC sample size of 42,267. The male and the OC groups were then size matched to the non-OC group. A breakdown of the final number of patients prescribed each brand of OC can be found in Table 2.

Subsequently, we queried the database for lower-extremity MTI diagnoses in these groups (Table 3). Patients who used or were prescribed hormone supplements or had multiple injuries at the same time were excluded from this study. Recall that our main outcome for the analysis is the percentage of MTI relative to the total orthopedic indications in the group of patients. This normalization procedure was chosen because the M30Ortho dataset only includes patients with orthopedic indications.

Statistical analysis. Statistical analysis was carried out within the PearlDiver platform, which utilizes the open-source R software, and in GraphPad Prizm 9.1.1. First, a binary logistic regression was used to estimate the unadjusted odds ratio (OR) and 95% confidence interval (CI) of non-OC and OC on MTI development. Subsequently, a multiple logistic regression model was used to control the potential confounders, including, age, region, Charlson comorbidity index (CCI), and BMI, to assess the effect of non-OC and OC use on MTI development, thus estimating an adjusted OR (aOR) and 95% CI. A P value of less than 0.05 was considered statistically significant.

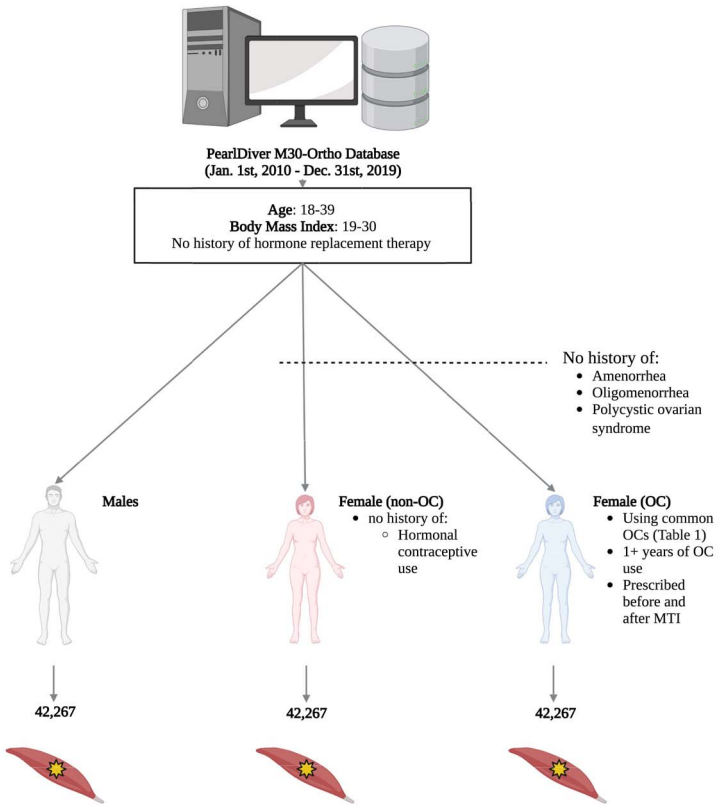

FIGURE 1—Schematic of PearlDiver query. Created with BioRender.com.

Chi-square testing was used to determine if significant differences in MTI percentage existed ($\alpha = 0.05$) between age-groups (non-OC vs OC) based on age categories defined by PearlDiver (18–34,and,35-39). *Post hoc* chi-square tests were used to determine statistically significant differences between male versus non-OC, male versus OC, and non-OC versus OC groups, with a Bonferroni correction, where a new α is calculated to account for multiple comparisons:

$$\alpha_{new} = \frac{1 - \left(1 - \alpha^{df}\right)}{c} = 0.0325$$

where df is degrees of freedom and c is number of comparisons.

RESULTS

Patient characteristics. The distribution of BMI and age is reported in detail in Table 4. Briefly, males had more patients in the overweight category compared with female groups, whereas the female groups had similar distributions. However, the distribution of age was similar between all three groups. In the cohort of 42,267 males, a percentage of 3.49% (1476 individuals) experienced an MTI, whereas non-OC and OC groups experienced significantly less MTI, 2.55% (1078 individuals, $P < 0.001$) and 0.55% (231 individuals, $P < 0.001$), respectively (Table 5). Because of limitations in ICD coding, only a subset of the MTI had their location reported: 46.21% for males, 47.77% for non-OC, and 45.02% OC. In patients with such MTI, males had 210 upper (30.79%) and 472 lower (69.21%) leg MTI, whereas non-OC had 223 (43.30%) and 292 (56.70%) of these injuries, and OC had 71 (68.27%) and 33 (31.73%; Table 6). Chi-square testing revealed a significant difference in injury location between all the groups ($P < 0.001$). *Post hoc* chi-square testing revealed a significant difference in injury location between all groups ($P < 0.001$).

Unadjusted association of MTI and OC use. The logistic regression revealed that OC females were less likely (OR = 0.15, 95% CI = 0.13–0.17, $P < 0.001$) (OR = 0.72, 95% CI = 0.67–0.78) to develop MTI followed by non-OC women (OR = 0.72, 95% CI = 0.67–0.78, $P < 0.001$) when compared with males (Table 5).

Adjusted association of MTI and OC use. When potential confounders were controlled for (age, BMI, CCI, region), the multiple logistic regression showed that the OC group was less likely to develop MTI (aOR = 0.15, 95% CI = 0.13–0.18, $P < 0.001$) followed by female with noncontraception (aOR = 0.74, 95% CI = 0.68–0.80, $P < 0.001$) when we compared with the matched male population. The effect was

TABLE 1. Combination OC pills with dosages used in the PearlDiver query.

Brand Name	Progestin (mg)	EE (mg)
Monophasic		
Apri[a]	Desogestrel (0.15)	0.03
Aviane[a]	Levonorgestrel (0.10)	0.02
Balcoltra[a]	Levonorgestrel (0.10)	0.02
Beyaz[a]	Drospirenone (3)	0.02
Cryselle[a]	Norgestrel (0.3)	0.03
Gianvi[a]	Drospirenone (3)	0.02
Junel Fe[a] 1–20/1.5–30	Norethindrone acetate (1/1.5)	0.02/0.03
Kelnor[b] 1–35/1–50	Ethynodiol diacetate (1)	0.035/0.05
Levora[a]	Levonorgestrel (0.15)	0.03
Loestrin 24 FE[a]	Norethindrone acetate (1)	0.02
Low Ogestrel[a]	Norgestrel (0.3)	0.03
Microgestin[c]	Norethindrone (1)	0.02
Mononessa[b]	Norgestimate (0.25)	0.035
Necon[a]	Norethindrone (1)	0.035
Nortrel[b]	Norethindrone (1)	0.035
Ocella[a]	Drospirenone (3)	0.03
Ogestrel[b]	Norgestrel (0.5)	0.05
Portia[a]	Levonorgestrel (0.15)	0.03
Previfem[a]	Norgestimate (0.25)	0.035
Safyral[a]	Drospirenone (3)	0.03
Yasmin 28[a]	Drospirenone (3)	0.03
Yaz[a]	Drospirenone (3)	0.02
Zarah[b]	Drospirenone (3)	0.03
Zovia[a] 1-35E/1-50E	Ethynodiol diacetate (1)	0.035/0.05
Biphasic		
Azurette[a]	Desogestrel (0.15, 21 d)	0.02 (21 d), 0.01 (5 d)
Kariva[a]	Desogestrel (0.15, 21 d)	0.02 (21 d), 0.01 (5 d)
Triphasic		
Caziant[b]	Desogestrel, 0.1 (7 d), 0.125 (7 d), 0.15 (7 d)	0.025
Ortho-Novum[a]	Norethindrone, 0.5 (7 d), 0.75 (7 d), 1.0 (7 d)	0.035
Trinessa[a]	Norgestimate, 0.18 (7 d), 0.215 (7 d), 0.25 (7 d)	0.035
Trivora 28[a]	Levonorgestrel, 0.05 (6 d), 0.075 (5 d), 0.125 (10 d)	0.03 (6 d), 0.04 (5 d), 0.030 (10 d)
Velivet[b]	Desogestrel, 0.1 (7 d), 0.125 (7 d), 0.15 (7 d)	0.025
Four-phasic		Estradiol valerate (mg)
Natazia[a]	Dienogest, 0 (2 d), 2 (5 d), 3 (17 d), 0 (2 d)	3 (2 dd), 2 (5 d), 17 (17 d), 2 (2 d)

Progestin and EE dosages reported from the following sources: [a] Rxlist.com, [b] Drugs.com, [c] Webmd.com.

TABLE 2. The breakdown of the number of patients taking each brand of OC in the OC group.

Monophasic	Patients	Biphasic	Patients	Triphasic	Patients	Four-Phasic	Patients
Apri	2035	Azurette	710	Caziant	83	Natazia	220
Aviane	2746	Karvia	915	Ortho-Novum	33		
Balcoltra	37			Trinessa	5377		
Beyaz	768			Trivora 28	451		
Cryselle	1657			Velivet	166		
Gianvi	1942						
Junel	2196						
Kelnor 1/35	228						
Kelnor 1/50	2						
Loestrin 24 FE	4993						
Low Ogestrel	1613						
Microgestin	2236						
Mononessa	3419						
Necon	1613						
Nortrel	1122						
Ocella	1945						
Ogestrel	121						
Portia	748						
Previfem	1450						
Safyral	142						
Yasmin 28	282						
Yaz	2205						
Zarah	444						
Zovia 1/35E	308						
Zovia 1/50E	60						
Total	34312		1625		6110		220
Percentage	81.18		3.84		14.46		0.52

TABLE 3. A list of international classification of diseases codes used in the database query.

ICD-9/ICD-10/CPT Codes Used in Queries				
ICD-9-D-8448	**ICD-9-D-8449**	**ICD-9-D-8438**	**ICD-9-D-8439**	**CPT-11975**
ICD-10-D-S76211A	ICD-10-D-S76211D	ICD-10-D-S76211S	ICD-10-D-S76212A	CPT-11976
ICD-10-D-S76212D	ICD-10-D-S76212S	ICD-10-D-S76219A	ICD-10-D-S76219D	CPT-11977
ICD-10-D-S76219S	ICD-10-D-S76311A	ICD-10-D-S76311D	ICD-10-D-S76311S	CPT-A4260
ICD-10-D-S76312A	ICD-10-D-S76312D	ICD-10-D-S76312S	ICD-10-D-S76319A	CPT-A4261
ICD-10-D-S76319D	ICD-10-D-S76319S	ICD-10-D-S76811A	ICD-10-D-S76811D	CPT-A4264
ICD-10-D-S76811S	ICD-10-D-S76812A	ICD-10-D-S76812D	ICD-10-D-S76812S	CPT-A4266
ICD-10-D-S76819A	ICD-10-D-S76819D	ICD-10-D-S76819S	ICD-10-D-S76911A	CPT-A4267
ICD-10-D-S76911D	ICD-10-D-S76911S	ICD-10-D-S76912A	ICD-10-D-S76912D	CPT-A4268
ICD-10-D-S76912S	ICD-10-D-S76919A	ICD-10-D-S76919D	ICD-10-D-S76919S	CPT-A4269
ICD-10-D-S86111A	ICD-10-D-S86111D	ICD-10-D-S86111S	ICD-10-D-S86112A	CPT-J7296
ICD-10-D-S86112D	ICD-10-D-S86112S	ICD-10-D-S86119A	ICD-10-D-S86119D	CPT-J7300
ICD-10-D-S86119S	ICD-10-D-S86211A	ICD-10-D-S86211D	ICD-10-D-S86211S	CPT-J7301
ICD-10-D-S86212A	ICD-10-D-S86212D	ICD-10-D-S86212S	ICD-10-D-S86219A	CPT-J7302
ICD-10-D-S86219D	ICD-10-D-S86311A	ICD-10-D-S86311D	ICD-10-D-S86311S	CPT-J7303
ICD-10-D-S86312A	ICD-10-D-S86312D	ICD-10-D-S86312S	ICD-10-D-S86319A	CPT-J7304
ICD-10-D-S86319D	ICD-10-D-S86319S	ICD-10-D-S86811A	ICD-10-D-S86811D	CPT-J7306
ICD-10-D-S86811S	ICD-10-D-S86812A	ICD-10-D-S86812D	ICD-10-D-S86812S	CPT-J7307
ICD-10-D-S86819A	ICD-10-D-S86819D	ICD-10-D-S86819S	ICD-10-D-S86911A	CPT-Q9984
ICD-10-D-S86911D	ICD-10-D-S86911S	ICD-10-D-S86912A	ICD-10-D-S86912D	CPT-S4989
ICD-10-D-S86912S	ICD-10-D-S86919A	ICD-10-D-S86919D	ICD-10-D-S86919S	CPT-S4993

significantly similar even when the confounders were considered (Table 5).

Subgroup analysis based on age criteria. When non-OC and OC patients were compared by age-group, chi-square testing revealed that OC patients 20–24 yr old had a significantly higher percentage of MTI. The 30- to 34-yr OC users had a lower percentage of MTI and were treading toward significance ($P = 0.034$) at 14.72% (OR = 0.66, 95% CI = 0.45–0.97), whereas the 35-to-39-yr groups showed a significantly lower percentage of MTI at 13.85% (OR = 0.59, 95% CI = 0.41–0.90, $P < 0.03$) for the group (Table 7).

DISCUSSION

In this retrospective study, we analyzed patient insurance claims from PearlDiver, a large for-fee national database, to determine if sex and the use of OC in females is associated with the percentage of MTI to total injuries. To the authors' knowledge, this is the first database study to characterize the proportion of MTI to total injuries between males, female OC users, and female non-OC users. When compared with males, and after controlling for age, BMI, CCI, and region, females in general (both OC and non-OC users) had a significantly lower percentage of MTI. Furthermore, we found that females using OC incurred a significantly lower percentage of MTI when compared with females not taking OC, suggesting that the sex hormone milieu (lower concentrations of endogenous E2 and progesterone through exposure to exogenous EE and progestin) may be associated with a smaller percentage of MTI compared with overall injuries.

In the female cohorts, MTI location and interaction with age were also investigated. This study showed statistically significant differences in the ratio of upper to lower leg injuries between the three groups. Females using OC exhibited a significantly higher percentage of upper leg injuries compared with the male and non-OC groups. Males and non-OC females had primarily lower leg injuries, with males having a higher percentage. However, caution should be taken when trying to interpret these results because less than half of the reported MTI had locations noted.

Taking age into consideration, females taking OC 20–24 yr old had a significantly higher percentage of MTI compared with the non-OC group. Only females 30 yr and older taking OC had a lower percentage MTI compared with total injuries, compared with the non-OC group. Interestingly, in a recent examination by DeFroda et al. (32), OC usage was found to be most protective against ACL tears in 15- to 19-yr-old patients. By contrast, bone mineral density in 15- to 19-yr-old subjects was negatively correlated with OC usage (33). These findings seem to indicate a tissue-specific differential effect of OC.

A recent epidemiological examination by Eckard and colleagues (11) revealed a higher rate of quadriceps injury in female collegiate soccer players than to male collegiate soccer players.

TABLE 4. The distribution of age and BMI for each group.

		Male (%)	Non-OC (%)	OC (%)
Age	18–19	5.67	5.78	5.48
	20–24	22.75	22.03	22.05
	25–29	27.75	26.05	26.88
	30–34	23.72	24.22	24.16
	35–39	20.11	21.92	21.43
BMI	19.0–24.9	39.42	44.94	48.17
	25.0–30.9	60.58	55.06	51.83

TABLE 5. Percentage of MTI to total injuries.

	MTI	% MTI	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P* Value
Male	1476	3.49	–	–	–
Non-OC	1078	2.55	0.72 (0.67–0.78)	0.74 (0.68–0.80)	<0.001* <0.001#
OC	231	0.55	0.15 (0.13–0.17)	0.15 (0.13–0.18)	<0.001* <0.001#

Injuries in the non-OC and OC groups were compared with those of the male group to characterize MTI frequency differences between sexes. Females taking OC are less likely to develop MTI followed by female with noncontraception when we compared with the matched male population.

* *P* value from the unadjusted logistic regression.

P value from the multiple logistic regression (adjusted for age, BMI, CCI, and region).

TABLE 6. MTI locations by group.

Group	Percent of Group MTI with Location Reported	Upper Leg (% of Total MTI)	Lower Leg (% of Total MTI)	Total	*P* Value
Male	46.21	210 (30.79)	472 (69.21)	682	
Non-OC	47.77	223 (43.30)	292 (56.70)	515	<0.001* <0.001#
OC	45.02	71 (68.27)	33 (31.73)	104	<0.001* <0.001#

Chi-square test resulted in a significant difference between the proportions of upper to lower leg MTI between groups ($P < 0.001$). *Post hoc* chi-square revealed significant differences between all groups.

* Comparison to males.

Comparison between female groups.

Similarly, an examination of professional soccer players in Spain showed a higher incidence of quadriceps injuries (12) in female athletes compared with males. In high school basketball, female athletes were found to have a higher percentage of MTI during practice than male athletes (5). However, the literature linking MTI to sex is mixed. For example, Dalton et al. (13) reported a higher incidence of hamstring injury in males compared with females in soccer, baseball/softball, and indoor track, and Larruskain and colleagues (12) also showed that a higher percentage of hamstring, hip, and groin injuries were reported in male professional soccer players when compared with their female counterparts. Although it is likely that the sex disparity of injury is both sport specific and specific to the musculotendon structure involved, it is also possible that conflicting results in the literature are due to differences in study methodology such as injury tracking and reporting and injury exposure definitions (34).

Although the studies presented in the previous section (5,11–13,34) were focused on the athletic population, the sex signature of musculoskeletal injuries in the general population is not well reported. Our data seem to suggest that males, in the general population, may have more MTI compared with females, regardless of hormone status. Because of the nature of this study, we were unable to isolate the type of injury that occurred, i.e., whether the injury was in the muscle or tendon. Additionally, without records about the patients' participation in sports and exercise, it is difficult to make direct comparisons between the groups. For example, if one group had more exposure to sports/exercise, they may be at a higher risk of MTI but may have a lower percentage of MTI overall.

In the general population, it has been reported that male-to-female Achilles tendon injury ratios range from 2:1 to 12:1 (35). These observations are consistent with our findings albeit generalized to MTI at large. Our data indicate that there was a difference in the percentage of MTI compared with all orthopedic injuries between the female nonusers and users of OC. However, there is little information in the literature on MTI in females as a function of sex hormone status (e.g., during the menstrual cycle or OC use) to compare against. To the author's knowledge, one of the few (if not only) studies to report such data was carried out by Martin and colleagues (17), who examined injuries over the menstrual cycle of eumenorrheic professional soccer players. The injuries of interest included bone, joint/ligament, brain/spinal cord/peripheral nervous system, and muscle/tendon. Their work showed that MTI were almost twice as frequent during the late follicular phase (17) when E2 rises from its lowest to its peak concentration within a few days (36). Similar findings have been reported in studies focusing on ACL injuries (14,15).

Our study, although not examining the hormonal fluctuation over the menstrual cycle as in Martin et al. (17), involved a group with minimized fluctuations of endogenous hormones (users of OC), which allowed us to determine if fluctuating sex hormone concentrations were associated with a higher percentage of MTI. Although we were unable to determine the menstrual cycle phase of the non-OC users at the time of their injury, our findings suggest that OC use may contribute to a reduction of MTI. It must be acknowledged that this study also assesses the effect of exposure to exogenous hormones. It remains to be seen how exogenous hormones in OC act on the existing molecular/cellular pathways in muscle and tendon. For example, it has been suggested by a computational model that EE has a higher affinity to estrogen receptors than the natural ligand 17β-estradiol (37). To what extent these computational findings are corroborated with experimental data is yet to be seen. Furthermore, it is largely unknown if these exogenous hormones would elicit a stronger activation of estrogen receptors than endogenous 17β-estradiol. It will be important to determine the potency of the influence of sex hormones (endogenous and exogenous) on muscle and tendon, i.e., which tissue is affected more significantly by changes in the physiological levels of sex hormones.

The mechanisms that facilitate sex hormone–associated MTI at this point are unclear. However, there are several potential mechanisms in which sex hormone–associated injury could occur. It has been established that E2 can affect many characteristics of muscles and tendons. In skeletal muscle, E2 has been shown to affect contractility and structure. Phosphorylation of the myosin regulatory light chain increases both force and power output, causing a change in muscle contractility (22). It has been shown that E2-deficient postmenopausal women have reduced phosphorylation compared with age-matched men (38). If this effect holds in eumenorrheic women, it might be expected that injuries would increase during menses, for example, because of suboptimal contractility during sport. This proposition is, however, not supported by the reported literature on MTI (17). A recent meta-analysis shows that strength changes throughout the menstrual cycle are unlikely (39). Nevertheless, to what extent the regulatory light chain phosphorylation would be altered during the menstrual cycle or during OC use is still unclear.

TABLE 7. Percentage of patients experiencing an MTI according to OC usage and age-group.

Age	OC (% OC with MTI)	Non-OC (% Non-OC with MTI)	*P* Value
18–19	17 (7.36)	84 (7.79)	0.8
20–24	80 (34.63)	265 (24.58)	<0.03
25–29	68 (29.44)	241 (22.36)	0.08
30–34	34 (14.72)	240 (22.26)	0.034
35–39	32 (13.85)	248 (23.01)	<0.03
Total	231	1078	

Only the 20–24, the 30–34, and the 35–39 OC groups showed a significant difference in the proportion of MTI injuries.

OC use and its effects on protein synthesis in tendons and muscles has been examined and suggested as a potential mechanism that drive hormone-associated injuries. For example, estrogen is associated with the suppression of myofibrillar synthesis (22,40); muscular adaptation, via protein synthesis, to increased loading is important in preventing injuries (40). Myofibrillar proteins are classified as the proteins involved in contraction (e.g., myosin, actin, tropomyosin, troponin, etc.). However, recent studies investigating adaptations to resistance training showed an increase in muscle cross-sectional area (41–43). Furthermore, it is reported by Dalgaard et al. (41) that the change in the muscle cross-sectional area associated with OC usage was primarily driven by an increase in type I fiber cross-sectional area.

In the context of the noncontractile component of the musculotendon unit, the tendon, previous literature reported that OC use is associated with lower tendon collagen synthesis rates in response to exercise compared with eumenorrheic women (16,40,44). Furthermore, OC use has been linked to increased tendinopathy (45). However, in the current database study, we showed that the percent MTI was lower in the OC group compared with the non-OC group. Taken together, these opposing findings on the effect of OC use on the contractile/noncontractile components of the musculotendon unit are intriguing and likely indicate that our findings may be a manifestation of the net effect of OC use on both the active and the passive elements of the musculotendon unit.

Finally, the effects of E2 on the transition zone between muscle and tendon may be of interest. Muscle forces are transmitted to the tendon by way of the myotendinous junction (MTJ) (46). Muscle strains are most commonly located at the MTJ and present with small tears and swelling between the muscle and the tendon (47). Muscle fibers and tendon structures are both important for forming MTJs capable of counteracting the forces transmitted in physical activity and for preventing injury in the MTJ (48). As previously mentioned, E2 may modulate tendon collagen synthesis and incorporation (49). Acute changes in collagen synthesis or the incorporation of MTJ-specific collagens (collagen XXII) (50) over the menstrual cycle could have implications for injury and healing of the MTJ in females and contribute to differences in muscle strain injuries between non-OC and OC females as seen in the PearlDiver database.

Limitations. As with all studies, some limitations add difficulty to interpretations of the results. The most obvious limitation of our study is that the MOrtho30 PearlDiver database does not allow us to determine the susceptibility of the groups, only the percentage of orthopedic injuries in the group that are MTI. For example, data regarding the patient's physical activity levels, types of physical activity participation (e.g., recreational/competitive sport, regular exercise), or number of exposures (i.e., number of practices, games, exercise sessions) are not available. Without this information, we could not accurately assess the susceptibility of the groups to MTI. Furthermore, claims data for this patient population do not necessarily represent that of the general population because of the exclusion of certain patient populations, such as patients with BMIs greater than 30.9 ($kg \cdot m^{-2}$). Similarly, because of limitations in the PearlDiver database, we were not able to report race or ethnicity. Nevertheless, certain aspects of our sample, such as its size, broad age range, and geographic location, help mitigate this issue.

The accuracy of ICD diagnoses and coding cannot always be guaranteed. Codes will specify the general location of the injury but not the degree (grades 1–3) or the exact location (the muscle belly, muscle–tendon junction, or tendon) of the injury. Similarly, the mechanism of the MTI (noncontact or traumatic injury), onset (acute or chronic), or duration were not available through the PearlDiver database. Some of the data on injury in the PearlDiver database were likely acquired in urgent or emergency care settings where diagnoses like strains and sprains are often given without any evaluation by an orthopedic or sports medicine specialist or without confirmatory imaging (e.g., ultrasound, magnetic resonance imaging). These terms (strains and sprains) can be used as "bucket diagnoses" when a bone fracture has been ruled out as the driver for pain at presentation. Furthermore, less severe MTI may not have resulted in presentation to a healthcare facility and an eventual bill to the insurance company. Therefore, the number of diagnoses in each group may not reflect true MTI pathology.

Although our coding included patients with prescribed OC, OC usage adherence, dosage, and type were not available at the individual level. Also, not available in the database is information on whether the patient was actively taking their OC at the time of injury. The various dosages of EE and progestin (and type of progestin used) of the specified OC as well as their phase type (monophasic, biphasic, triphasic, and four-phasic) could have differential effects on MTI. Unfortunately, the overall number of the MTI in the OC group does not allow for the determination of the type of OC used by the injured patients. However, we were able to break down the brand/type usage of the 42,276 subjects in the OC group (Table 2) and saw that most (81%) patients were taking a monophasic OC.

An exploration that includes comprehensive medical records would likely provide a design to interrogate the effects between the different OC types. It is difficult to determine if the results seen in this study are a direct result of minimized fluctuations in endogenous sex hormones, chronic exposure to exogenous hormones, or a combination of both. It is worth noting that our search did not include patients using progestin-only contraceptives, such as pills, injections, subdermal implants, and intrauterine devices. It is unclear if there would be a differential effect on musculoskeletal injury between progestin-only contraceptives and combination OC containing EE. Future studies are needed to differentiate these potential effects on MTI. Despite these limitations, our study provides novel data on the effects of OC on MTI in females, a topic that has not been rigorously investigated.

CONCLUSIONS

In this study, we show that females are less likely to develop MTI to total injuries, when compared with males, with OC using females being least likely followed by non-OC females.

Much of the literature describing the epidemiology of MTI have been focused on athletes at the recreational (youth sports) and elite levels (college and professional). Our dataset represents a more general population with a similar age range to elite level athletes as studied in previous literature. This study adds to the emerging body of literature on musculoskeletal injuries that are associated with sex hormones but more specifically provides data on MTI, which has not been rigorously investigated.

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