REVIEW OPEN ACCESS

The Role of Sex Hormones in Cartilaginous Tissues: A Scoping Review

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ABSTRACT

Background: The use of sex hormones in the clinic for the management of musculoskeletal conditions is increasingly common. Despite this, the role of sex hormones in various joint tissues such as the intervertebral disc (IVD), temporomandibular joint (TMJ), and articular cartilage remains poorly understood. Here, we employ a database search strategy to critically examine the available literature in this field through a scoping review.

Methods: Using a 4-step protocol, primary research articles pertaining to sex hormones and the IVD, TMJ, or articular cartilage were identified and reviewed by two independent reviewers. ~3900 articles were identified in our initial search, and after review, ~140 were identified to be relevant to our tissues of interest and the effects of sex hormones.

Results: Within all joint tissues investigated here, there were limited investigations on the effects of testosterone. Studies reported here for these tissues indicate that sex hormones are likely beneficial in the context of age-associated joint diseases, but there are important limitations to how this translates to the clinic given that various animal models can display distinct responses to sex hormone exposure. Direct comparisons of sex hormone therapies are limited between biological sexes, but evidence indicates that the molecular responses are likely similar. Current evidence indicates that sex hormone exposure likely has anti-inflammatory effects within joint tissues at the level of gene and protein expression, but the mechanism is unknown.

Conclusion: Sex hormones such as testosterone and estrogen play an important role in inflammatory signaling within joint tissues, which could lead to novel interventions within the clinic for joint degeneration. However, understanding the biological mechanisms of hormones in these distinct tissues, between sexes, and with age is imperative for their proper implementation.

1 | Introduction

1.1 | Rationale

Musculoskeletal disorders are a tremendous burden on human health and health care systems around the world. Low back pain, for example, is the leading cause of years lived with disability worldwide [1]; and is often associated with degeneration of the intervertebral disc (IVD), the fibrocartilaginous joint located between joints of the spine. Osteoarthritis, also a leading cause of disability, is a heterogeneous disease affecting numerous joints, including the knee and hands. Although the cell types and overall tissue structure differ between articular and intervertebral joints, disc degeneration and osteoarthritis share numerous hallmarks and molecular pathways [2]. Despite their prevalence, both conditions lack disease-modifying treatments. Of note, the incidence

and severity of both IVD degeneration and osteoarthritis have been associated with sex differences [1, 3], and, specifically, the loss of endogenous sex hormones [4, 5]. Men display a higher prevalence of back pain until the fifth decade of life, after which women have a higher prevalence than men, a change likely corresponding to the onset of menopause [6, 7] and acute loss of sex hormone production in females. Menopause has also been linked to the progression of osteoarthritis, but there are mixed results on the direct effects of sex hormones on the health of the joint [8]. While the effects of sex hormones in bone are widely studied, their effects on joint cells and tissues are poorly understood, despite likely correlations between changes in sex hormone production and disease in cartilaginous tissues. The aim of this scoping review was to summarize the available literature on the effects of sex hormones on joint tissues to contextualize their effects and suggest future directions for the field. While sex hormones are important regulators of bone, this topic has been extensively reviewed [9–14] and as such will not be addressed here, aside from subchondral bone as it relates to joint health and homeostasis.

1.2 | Research Questions

(1) What are the roles of sex hormones within various joint tissues (intervertebral disc, temporomandibular joint, and articular cartilage)? (2) Are the roles of sex hormones dependent on biological sex? (3) Do these joints respond differently to hormone stimulation?

2 | Methods

2.1 | Search Strategy

A four-step protocol using Covidence software to search multiple databases and identify studies of interest was applied. Then, two reviewers (JLH, AJH, or JF) independently screened titles and abstracts for inclusion eligibility. Discrepancies in agreement for inclusion were discussed individually and were then included or excluded based on mutual decision. Cohen's Kappa test for Title and Abstract screening was 0.745. Selected articles (221) were then retrieved for full-text review and screened independently by two reviewers (JLH, AJH, or JF). Papers without English translations and papers that were unobtainable online were excluded from the study ($N = 12$). Details including study design, study subjects, and sample size, methodology, and results from each study were extracted and summarized.

2.2 | Eligibility Criteria

This review included peer-reviewed primary research articles that describe the effects of sex hormone supplementation or loss of endogenous production in articular cartilage, IVD, and the temporomandibular joint. No restrictions were set based on species, age, sex, ethnicity, or health status.

2.3 | Information Sources

Only qualitative and quantitative articles from peer-reviewed journals were considered. Narrative reviews, letters, and editorials were screened to ensure that original sources were included. No restrictions were set regarding the original publication language or year of publication. Four electronic databases were searched: PubMed, Web of Science, MEDLINE Ovid, and Scopus. These databases encompass a broad overview of literature pertaining to biomedicine, health, life, and physical sciences. Exclusion criteria included removal of secondary literature or opinion articles, papers that examined the effects of sex hormones on only bone (except for subchondral bone), and papers that did not test agonism or antagonism of sex hormones in the context of joint health.

2.4 | Data Charting Process

A single reviewer charted data from each of the included full text articles. Data charted included citation information, the study design, cell and animal models used, major interventions or surgical models used, and their general outcomes.

2.5 | Synthesis of Results

Data from the charting process was tabulated and organized by tissue or cell types (fibrocartilage or articular cartilage) and study design. For each tissue of interest, the sex hormones studied were tabulated to create an overview of their roles in each respective tissue.

3 | Results

3.1 | Selection of Sources of Evidence

We identified 3855 articles after the four-database search (Web of Science, PubMed, Ovid Medline, Scopus) on April 16, 2024. After removal of duplicate articles, 3622 citations were evaluated by two independent reviewers in a screening process assessing the title and abstracts, followed by full-text review. Inclusion criteria for this study required primary research articles addressing the loss of, supplementation, or treatment with sex hormones in vitro or in vivo and joint tissues. This included treatment of sex hormones on joint cells and tissues, in addition to models of ovariectomy/orchidectomy, and sex hormones in joint disease. Cohen's kappa reported a 0.78 agreement in Title and Abstract screening, and 0.48 for the full-text review. At both stages, discrepancies in the agreement were discussed after the independent review to determine eligibility. After compiling the search results, there were 148 papers identified in this search (Figure 1).

We categorized the papers by joint of interest: the intervertebral disc (Table 1), the temporomandibular joint (Table 2), and the articular cartilage (Table 3).

3.2 | The Effects of Sex Hormones on the IVD

3.2.1 | Study Design

Various study designs were employed, including non-randomized experimental (39), cohort (3), case control (2), randomized controlled trial (8), case series (1), questionnaires (1), and cross-sectional (1) studies. Publications by year are reported for all studies

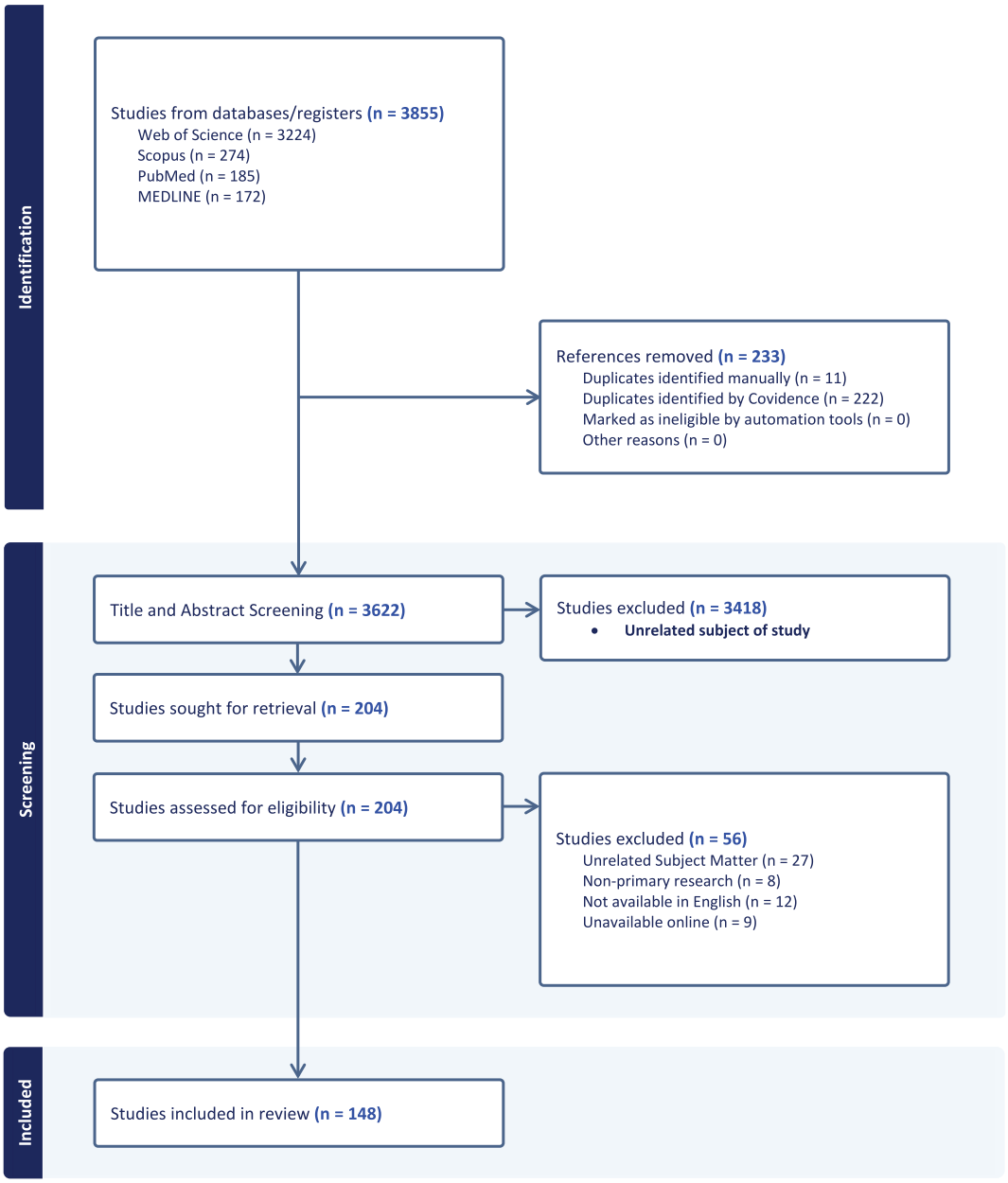

FIGURE 1 | PRISMA flow diagram for article retrieval and selection for inclusion. Primary research articles related to the role of sex hormones and IVD, TMJ, and articular cartilage homeostasis were identified through multiple databases. Studies were screened by two independent reviewers, which identified 148 studies for this review.

identified (Figure 2A). The research typically focused on the lumbar spine using cell or organ culture (23), or in vivo analyses (33). Animal models used varied based on study design. Experimental studies used mouse, rat, rabbit, canine, bovine, and human cells or tissues, while questionnaire or cohort studies assessed human patients attending clinics or human participants (Figure 2B).

3.2.2 | Distribution of Biological Sex, Age, and Hormones Studied

Biological sex of the model systems was not evenly distributed, as females were more frequently studied (52%) compared to males (18%). Some studies used both biological sexes (21%) and a small proportion did not disclose biological sex (9%) (Figure 2C). Interventions used in these studies were primarily centered around estrogen removal, replacement, or use of estrogen agonists and antagonists (48). Three studies directly investigated testosterone exposure [15, 30, 32]. Some studies also investigated menopause-associated changes (4). Age distribution varied from juvenile animal models to middle-aged human (40–60 years old) individuals.

3.2.3 | Key Findings: IVD

Literature examining the role of sex hormones on the IVD focused on each of its tissue constituents: the nucleus pulposus (NP), annulus fibrosus (AF), and cartilage endplates (CEP). Of these, studies investigated changes in tissue hydration, apoptosis,

TABLE 1 | Included articles for the intervertebral disc: information and study design.

First author	Year	Study design	Species (strain)	Tissue/celltype	Anatomical region	Biological sex	Age of subject	Primary interventions or assessment
Paatsama [15]	1969	Non-randomized experimental study	Canine	IVDs	Lumbar spine	Male and female	1 week to 10 months	Testosterone and E2
Brynhildsen [16]	1998	Questionnaire	Human	Low back pain	Lumbar spine	Female	40–69 years	HRT
Gruber [17]	2002	Non-randomized experimental study	Human	IVD cell culture	Lumbar spine	Male and female	32–46 years	E2
Wang [18]	2004	Non-randomized experimental study	Rats (Sprague Dawley)	IVD	Lumbar IVDs	Female	3 months	OVX
Baron [19]	2005	Cohort study	Human	IVD	T12-L4	Female	~50 ± 8 years	HRT
Muscat Baron [20]	2007	Randomized controlled trial	Human	IVD	T12-L3	Female	Post-menopausal	HRT
Gambacciani [21]	2007	Cross sectional study	Human	IVD	IVDs (T12-L4)	Female	53 ± 14 years	Pre-, menopausal, and post-menopausal
Li X [22]	2008	Non-randomized experimental study	Bovine	Nucleus pulposus and annulus fibrosus cells	Caudal IVDs	NA	15–18 months	Resveratrol
Zhang [23]	2009	Non-randomized experimental study	Rats (Sprague Dawley)	Facet joint	Lumbar spine	Female	3 months	E2 and OVX
Baron [24]	2009	Randomized controlled trial	Human	IVD	T2-L3	Female	Pre- and postmenopausal	HRT
Rowas [25]	2012	Non-randomized experimental study	Mice (C57BL/6)	IVD	Lumbar spine	Male and Female	3 months	Estrogen agonist (diethylbestrol)
Yang [26]	2013	Non-randomized experimental study	Rats (Sprague Dawley)	Nucleus pulposus cells	Lumbar spine	Male	2 months	E2

(Continues)

TABLE 1 | (Continued)

First author	Year	Study design	Species (strain)	Tissue/celltype	Anatomical region	Biological sex	Age of subject	Primary interventions or assessment
Song [27]	2014	Non-randomized experimental study	Human	IVD	Lumbar spine	Male and female	65–77 years	Aging
Wang [28]	2014	Non-randomized experimental study	Rats (Sprague Dawley)	Nucleus pulposus and annulus fibrosus cells	Lumbar spine	Male	5–8 weeks	E2
Lou [29]	2014	Randomized controlled trial	Human	IVDs	Lumbar spine	Female	56.3 ± 12.9 years	Pre-, menopausal, and post-menopausal
Bertolo [30]	2014	Randomized controlled trial	Human	Nucleus pulposus cells	Cervical, thoracic and lumbar spine	Male and female	25–57 years	Testosterone
Wang [31]	2015	Cohort study	Human	IVD	Lumbar spine	Male and female	> 64 years	Aging
Dubick [32]	2015	Case series	Human	Low back pain	Lumbar spine	Male and female	58 ± 11 years	Testosterone and growth hormone
Ning [33]	2016	Non-randomized experimental study	Rats (Sprague Dawley)	Nucleus pulposus cells	Lumbar spine	Male	~5–8 weeks (~200-220 g)	E2
Wang [34]	2016	Non-randomized experimental study	Human	Nucleus pulposus cells	NA	NA	NA	E2
Yang [35]	2016	Non-randomized experimental study	Rats (Sprague Dawley)	Nucleus Pulposus Cells	Lumbar spine	Male	2 months	E2
Zhao [36]	2016	Non-randomized experimental study	Rats (Wistar)	Annulus fibrosus	Lumbar spine	Male	~5–8 weeks (~200 g)	E2
Jia [37]	2016	Non-randomized experimental study	Rats (Sprague Dawley)	IVD	Lumbar spine	Female	3 months	E2, PTH and OVX

(Continues)

TABLE 1 | (Continued)

First author	Year	Study design	Species (strain)	Tissue/celltype	Anatomical region	Biological sex	Age of subject	Primary interventions or assessment
Wei [38]	2016	Non-randomized experimental study	Human	Nucleus pulposus cells	Lumbar spine	Male and female	41 ± 15 years	ER agonists
Chatha [39]	2016	Randomized controlled trial	Rabbits (unidentified strain)	Annulus fibrosus injury	NA	Male	NA	Estradiol dipropionate
Lou [40]	2017	Randomized controlled trial	Human	IVD	Lumbar spine	Male and female	68.4 ± 10.9 (female) and 66.8 ± 12.1 (male)	Aging
Li [41]	2017	Non-randomized experimental study	Rats (Sprague Dawley)	IVD organ culture and nucleus pulposus cells	Lumbar spine	Male	12 weeks	E2
Song [42]	2017	Non-randomized experimental study	Human	NP tissues	L4/5 and L5/S1	Female	69.3 ± 2.6 years	E2 and Substance P
Ao [43]	2018	Non-randomized experimental study	Rats (Sprague Dawley)	Nucleus Pulposus cells	Lumbar Spine	Male	6–8 weeks	E2
Chen [44]	2018	Non-randomized experimental study	Rats (Sprague Dawley)	IVD	Caudal IVDs	Female	3 months of age	E2
Sheng [45]	2018	Randomized controlled trial	Human	IVD and cartilage endplates	Lumbar spine	Male and Female	39 ± 11 years	E2
Jin [46]	2018	Non-randomized experimental study	Rats (Sprague Dawley)	IVD	Lumbar spine	Female	6 weeks	E2 and OVX
Liu [47]	2018	Non-randomized experimental study	Rats (Sprague Dawley)	IVD	Caudal IVDs	Female	3 months	E2 and OVX
Sheng [45]	2018	Non-randomized experimental study	Rats (Sprague Dawley)	Cartilage endplate cells	NA	Female	5–8 weeks	E2 and OVX

(Continues)

TABLE 1 | (Continued)

First author	Year	Study design	Species (strain)	Tissue/celltype	Anatomical region	Biological sex	Age of subject	Primary interventions or assessment
Wu [48]	2018	Non-randomized experimental study	Mice (C57BL/6)	Facet Joint	Lumbar Spine	Female	12 weeks	OVX
Xiao [49]	2018	Non-randomized experimental study	Mice (C57BL/6)	IVD	Lumbar spine	Female	8 weeks	OVX
Wen [50]	2019	Non-randomized experimental study	Human	Nucleus pulposus cells	Lumbar spine	Male and Female	59 ± 7.2 years	Beta-ecdysterone
Guo [51]	2019	Non-randomized experimental study	Rats (Sprague Dawley)	Nucleus pulposus cells	Lumbar IVDs	Male	2 months	E2 and ER antagonist
Liu [52]	2019	Non-randomized experimental study	Rats (Sprague Dawley)	IVD	Cranial	Female	3 months	HRT and OVX
Zhang [53]	2019	Non-randomized experimental study	Rats (Sprague Dawley)	IVD	Lumbar spine	Female	3 months	OVX
Cai [54]	2020	Non-randomized experimental study	Human	Nucleus Pulposus cells	Lumbar spine	Male and Female	43 ± 6 years	E2
Gao [55]	2020	Non-randomized experimental study	Human	Nucleus Pulposus cells	NA	NA	NA	E2
Bai [56]	2021	Non-randomized experimental study	Human	Nucleus pulposus cells	NA	NA	NA	E2
Song [57]	2021	Randomized controlled trial	Human	NP tissue	NA	NA	28–45 years	E2
Song [58]	2021	Non-randomized experimental study	Mice (C57BL/6)	Nucleus pulposus	Lumbar spine	Female	8 weeks	E2 and OVX

(Continues)

TABLE 1 | (Continued)

First author	Year	Study design	Species (strain)	Tissue/celltype	Anatomical region	Biological sex	Age of subject	Primary interventions or assessment
Tucci [59]	2021	Non-randomized experimental study	Rats (Sprague Dawley)	IVD	Lumbar spine	Female	3 months	E2 and OVX
Tian [60]	2021	Non-randomized experimental study	Rats (Sprague Dawley)	IVD	Caudal IVDs	Female	4, 8, and 12 weeks	E2 and OVX and IVD puncture
Sun [61]	2021	Non-randomized experimental study	Rats (Sprague Dawley)	IVD	Lumbar spine	Female	3 months	ER agonists and OVX
Zhao [62]	2021	Case control study	Human	IVD	Lumbar Spine	Female	62.40 ± 10.64 years	OVX Patients
Bhadouria [63]	2022	Non-randomized experimental study	Mice (C57BL/6)	IVD	Lumbar spine	Female	4 and 22 months	Raloxifene
Li [64]	2022	Case control study	Human	IVD	Lumbar spine	Female	47 ± 6 years	Tamoxifen
Heuch [65]	2023	Cohort study	Human	Low back pain	Lumbar spine	Female	40–69 years	Aging
Widmayer [66]	2023	Non-randomized experimental study	Bovine	IVD	Caudal IVDs	Male	12–24 months	E2 and vibration
Stevenson [67]	2023	Non-randomized experimental study	Human	IVD	Lumbar Spine	Female	55.4 years	E2, postmenopausal
Elmounedi [68]	2023	Non-randomized experimental study	Rats (Sprague Dawley)	IVD	Lumbar spine	Female	3 months	OVX
Song [69]	2023	Non-randomized experimental study	Mice (C57BL/6)	Spinal cord	Lumbar spine	Female	18 weeks	OVX and diarylpropionitrile

Abbreviations: E2, 17beta-estradiol; ER, estrogen receptor; HRT, hormone replacement therapy; IVD, intervertebral disc; OCX, orchidectomy; OVX, ovariectomy; PTH, parathyroid hormone.

TABLE 2 | Included articles for the temporomandibular joint: information and study design.

First author	Year	Study design	Species (strain)	Tissue or cell type[a]	Biological sex	Age of subject	Primary interventions or assessment
Aufdemorte [70]	1986	Non-randomized experimental study	Baboon	Articular disc, condylar surface	Female	19.1 years	OVX and tritiated HRT
Orajarvi [71]	2011	Non-randomized experimental study	Rats (Sprague Dawley)	Condylar cartilage	Female	2 months	OVX and diet hardness
Orajarvi [72]	2012	Non-randomized experimental study	Rats (Sprague Dawley)	Condylar Cartilage	Female	5 and 14 months	OVX and diet hardness
Robinson [73]	2017	Non-randomized experimental study	Mice (C57BL/6)	Condylar cartilage	Male	49 days	ERα KO
Abubaker [74]	1996	Non-randomized experimental study	Rats (Wistar)	Articular disc	Male and female	3 weeks	OVX or OC and HRT
Yamada [75]	2003	Non-randomized experimental study	Rats (Wistar)	Synovium, articular disc, and mandibular condyle	Male	4 weeks	ER localization
Min [76]	2007	Non-randomized experimental study	Mice (ICR)	Condylar cartilage	Female	4 months	OVX
Puri [77]	2009	Non-randomized experimental study	Rats (Sprague Dawley)	Synovium, articular disc, and mandibular condyle	Female	7 months	OVX and E2
Wu [78]	2010	Non-randomized experimental study	Rats (Sprague Dawley)	Whole joint	Female	Adult	OVX and E2
Madani [79]	2013	Cross sectional study	Human	Blood from TMJD patients	Female	20–40 years	TMJ disease
Chen [80]	2014	Non-randomized experimental study	Rats (Sprague Dawley)	Condylar cartilage, subchondral bone	Female	7 months	OVX
Chen [81]	2014	Non-randomized experimental study	Mice (C57BL/6)	Condylar cartilage	Female	21 days	OVX, ERβ KO, and HRT
Stemig [82]	2015	Non-randomized experimental study	Human	N/A	Male and Female	N/A	Genotypic association with TMJD
Figueroba [83]	2015	Non-randomized experimental study	Rats (Wistar)	Condylar cartilage, synovium	Male and Female	3 months	OCX and OVX
Nicot [84]	2016	Cohort study	Human	N/A	Male and Female	14–37 years	Genotypic association with TMJD

(Continues)

TABLE 2 | (Continued)

First author	Year	Study design	Species (strain)	Tissue or cell type[a]	Biological sex	Age of subject	Primary interventions or assessment
Fanton [85]	2017	Non-randomized experimental study	Rats (Wistar)	Nervous system	Male and Female	3 months	OVX or OCX
Ahmad [86]	2018	Randomized controlled trial	Mice (C57BL/6)	TMJ fibrocartilage	Female	12 weeks	ERα and ERβ overexpression and knockdown
Flake [87]	2006	Non-randomized experimental study	Rats (Sprague Dawley)	TMJ blood vessels	Male and Female	N/A	OVX and HRT
Wang [88]	2013	Non-randomized experimental study	Rats (Sprague Dawley)	Condylar cartilage, subchondral bone	Female	N/A	OVX and HRT
Wu [89]	2019	Non-randomized experimental study	Mice (C57BL/6)	Condylar cartilage, subchondral bone	Female	8 weeks	OVX and mechanical stress
Zhang [90]	2023	Non-randomized experimental study	Mice (C57BL/6)	Condylar cartilage	Female	8 weeks	E2 deficiency and mechanical stress
Okuda [91]	1996	Non-randomized experimental study	Rats (Wistar)	Condylar cartilage, subchondral bone	Female	4 weeks	OVX
Yasuoka [92]	2000	Non-randomized experimental study	Rats (Wistar)	Condylar cartilage, subchondral bone	Female	4 weeks	OVX and hormone replacement
Hauru [93]	2024	Non-randomized experimental study	Rats (Sprague Dawley)	Condylar cartilage	Female	5 and 14 months	OVX, aging, HRT, dietary loading
Yu [52]	2019	Non-randomized experimental study	Rats (Sprague Dawley)	Condylar cartilage	Female	5 and 14 months	OVX, dietary loading
Sheridan [94]	1985	Non-randomized experimental study	Baboon	Condylar cartilage	Female	18–21	3H-estradiol-17 β

Abbreviations: E2, 17beta-estradiol; ER, estrogen receptor; HRT, hormone replacement therapy; IVD, intervertebral disc; KO, Knockout; OCX, orchidectomy; OVX, ovariectomy; PTH, parathyroid hormone.
[a]Anatomical location was the TMJ for all studies listed above.

TABLE 3 | Included articles for articular cartilage: information and study design.

First author	Year	Study design	Species (strain)	Tissue or cell type	Anatomical region	Biological sex	Age of subject	Primary interventions or assessment
DaSilva [95]	1994	Non-randomized experimental study	Mice (BALB/C) and rats (Wistar)	Articular cartilage	Femoral head	Male and Female	9–10 weeks (Mice), (160-180 g male rats, 150-160 g female rats)	OVX or OCX +/− HRT
Rasanen [96]	1999	Non-randomized experimental study	Rabbits (New Zealand White)	Articular cartilage	Femoral head	Female	18–23 weeks	OVX and HRT
Dai [97]	2006	Non-randomized experimental study	Guinea pigs (Dunkin Hartley)	Articular cartilage	Femoral condyle, tibial plateau	Female	32 months	OVX
Dayani [98]	1988	Non-randomized experimental study	Rabbits (Fauve de Bourgogne)	Primary chondrocytes	Long bones	Male and Female	15–25 and 40–60 days old	ER expression by articular cartilage cells
Osman [99]	2019	Non-randomized experimental study	Rats (Sprague Dawley)	Articular cartilage	Knee	Female	3–4 months	OVX and HRT
Tang [100]	2020	Non-randomized experimental study	Human	Primary chondrocytes	Knee	Male and Female	62–68 years	OA and arctigenin
Rosner [101]	1982	Non-randomized experimental study	Rabbits (New Zealand White)	Articular cartilage	Knee	Female	N/A	OVX
Corvol [102]	1987	Non-randomized experimental study	Rabbits (Fauve de Bourgogne)	Primary epiphyseal articular cells	Long bones	Male and Female	2–80 days	Age, sex hormone (testosterone, DHT, E2)
Tsai [103]	1993	Non-randomized experimental study	Rabbits (New Zealand White)	Articular cartilage	Lateral femoral condyle, patella	Female	N/A	OVX + E2
Turner [104]	1997	Non-randomized experimental study	Ewe	Articular cartilage	Femur and Tibia	Female	4–5 years	OVX

(Continues)

TABLE 3 | (Continued)

First author	Year	Study design	Species (strain)	Tissue or cell type	Anatomical region	Biological sex	Age of subject	Primary interventions or assessment
Claassen [105]	2002	Non-randomized experimental study	Pigs (gottingen miniature pigs)	Articular cartilage	Proximal wrist joint	Female	33 months	OVX, dietary Ca2+
Lee [106]	2003	Randomized controlled trial	Human	Primary chondrocytes	Knee	Female	55–84	E2
Hoegh-Andersen [107]	2004	Non-randomized experimental study	Rats (Sprague Dawley)	Articular cartilage	Knee	Female	5 and 7 months	OVX and SERM
Claassen [108]	2005	Non-randomized experimental study	Bovine	Articular Chondrocytes	Intertarsal joint	Female	2 and 7 years	E2
Claassen [109]	2006	Non-randomized experimental study	Bovine	Articular chondrocytes	Transverse tarsal joint	Female	N/A	E2, insulin, tamoxifen, ICI
Oshima [110]	2007	Non-randomized experimental study	Rats (Wistar)	Articular cartilage, subchondral bone	Femur	Male and Female	1 day, 1 week, 1 month, 3 month, 24 month	OVX, sex
Castaneda [111]	2010	Non-randomized experimental study	Rabbits (New Zealand White)	Articular cartilage	Knee	Female	8 months	OVX, glucocorticoid
Sniekers [112]	2010	Non-randomized experimental study	Mice (C3H/HeJ)	Articular cartilage, subchondral bone	Knee	Female	24 weeks	OVX, E2, bisphosphonate
Claassen [113]	2010	Non-randomized experimental study	Human	Articular Chondrocytes	Hip, knee, or ankle	Male and Female	28–85 years	E2
Bay-Jensen [114]	2011	Non-randomized experimental study	Rats (Sprague Dawley)	Articular cartilage	Knee	Female	6 months	OVX
Yang [115]	2012	Non-randomized experimental study	Rats (Sprague Dawley)	Bone, articular cartilage	Knee	Female	7 months	OVX, E2, progesterone

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TABLE 3 | (Continued)

First author	Year	Study design	Species (strain)	Tissue or cell type	Anatomical region	Biological sex	Age of subject	Primary interventions or assessment
Fontinele [116]	2013	Non-randomized experimental study	Rats (Wistar)	Articular cartilage	Tibial proximal epiphysis	Female	6 months	OVX, physical activity
Yan [117]	2014	Non-randomized experimental study	Guinea Pigs (Dunkin Hartley)	Articular cartilage, subchondral bone	Tibia	Female	41 months	Age
Liang [118]	2016	Non-randomized experimental study	Human	Primary chondrocytes	Knee	Female	> 53 years	E2, IL-1β
Lou [119]	2016	Non-randomized experimental study	Human	Articular cartilage	Knee	Female	36–83	Pain
Lee [120]	2017	Non-randomized experimental study	Rats (Sprague Dawley)	Articular cartilage	Knee	Female	8 weeks	OVX
Ge [121]	2019	Non-randomized experimental study	Mice (C57BL/6) and human chondrocytes	Articular cartilage	Knee	Male and Female	Mice; 10 weeks, human, 53–70 years	OVX
Hughbanks [122]	2021	Case control study	Human	Articular cartilage	Knee	Female	N/A	Total knee arthroplasty and ACL reconstruction
Li [123]	2022	Non-randomized experimental study	Mice (C57BL/6)	Articular cartilage, subchondral bone	Knee	Female	3 months	OVX, diet, physical activity, metformin
Huang [124]	2022	Non-randomized experimental study	Human and rabbit (New Zealand)	Primary chondrocytes	Knee	N/A	Adult	Psoralen
Polur [125]	2015	Non-randomized experimental study	Mice (C57BL/6)	Articular cartilage, subchondral bone	TMJ	Male and Female	21 days	ERβ KO

(Continues)

TABLE 3 | (Continued)

First author	Year	Study design	Species (strain)	Tissue or cell type	Anatomical region	Biological sex	Age of subject	Primary interventions or assessment
Richmond [126]	2000	Non-randomized experimental study	Monkeys (cynomolgus)	Articular cartilage	Knee	N/A	Adult	OVX, E2
Wluka [127]	2001	Non-randomized experimental study	Human	Articular cartilage	Knee	Female	> 50 years	Postmenopausal
Ham [128]	2002	Non-randomized experimental study	Monkeys (cynomolgus)	Articular cartilage, subchondral bone	Knee	Female	9.6–15.8 years	OVX, E2, soy phytoestrogen
Mouritzen [129]	2003	Randomized controlled trial	Human	Articular cartilage	Urinary CTX-II degradation products	Male and Female	20–87 years	Age, sex, menopause, HRT, and BMI
Cicuttini [130]	2003	Randomized controlled trial	Human	Articular cartilage	Patella	Female	> 50	ERT
Wluka [131]	2004	Non-randomized experimental study	Human	Articular cartilage	Tibia	Female	> 50	ERT
Ham [132]	2004	Non-randomized experimental study	Monkeys (Cynomolgus)	Articular cartilage	Knee	Female	10.7–13.6	OVX
Cake [133]	2005	Non-randomized experimental study	Ovine	Articular cartilage	Femoro-tibial joint	Female	7 years	OVX
Dai [134]	2005	Non-randomized experimental study	Guinea Pigs (Dunkin Hartley)	Articular cartilage	Tibial plateau	Female	2 months	OVX
Oestergaard [135]	2006	Non-randomized experimental study	Rats (Sprague Dawley)	Articular cartilage	Serum CTX-II degradatio product	Female	6 months	OVX + early/delayed E2
Kato [136]	2010	Non-randomized experimental study	Mice (C57BL/6)	Articular cartilage, primary chondrocytes	Knee	Female	4 and 15 months	ERα KO mice

(Continues)

TABLE 3 | (Continued)

First author	Year	Study design	Species (strain)	Tissue or cell type	Anatomical region	Biological sex	Age of subject	Primary interventions or assessment
Wei [137]	2011	Cross sectional study	Human	Articular cartilage	Knee	Female	50–80 years	Parity
Kavas [138]	2013	Non-randomized experimental study	Rats (Sprague Dawley)	Articular chondrocytes	Knee	N/A	N/A	Raloxifene
Hamdi [139]	2022	Non-randomized experimental study	Human	Articular chondrocytes	Knee	Male and Female	63–85 years	E2, raloxifene, enterolactone
Jiang [140]	2023	Non-randomized experimental study	Rats (Sprague Dawley)	Articular chondrocytes and subchondral osteoblasts	N/A	Female	6 months	OVX induced OA
Bei [141]	2020	Non-randomized experimental study	Rats (Sprague Dawley)	Articular cartilage, subchondral bone	Patello-femoral joint	Female	3 months	OVX, raloxifene
Ziemian [142]	2021	Non-randomized experimental study	Mice (C57BL/6)	Articular cartilage, subchondral bone, joint capsule	Knee	Female	26 weeks	ERα KO mice
Wang [143]	2016	Non-randomized experimental study	Rats (Sprague Dawley)	Articular cartilage	Knee	Female	10 months	OVX
Xu [144]	2019	Non-randomized experimental study	Rats (Sprague Dawley)	Articular cartilage, subchondral bone	Knee	Female	6 months	OVX, E2, SERM, raloxifene
Jin [145]	2017	Cohort study	Human	Articular cartilage	Knee	Male and Female	56.7–69.3 years	Symptomatic knee OA
Duan [146]	2021	Non-randomized experimental study	Rats (unidentified strain)	Articular cartilage	Knee	Female	6 months	ERα targeted knockdown (PROTAC)

(Continues)

TABLE 3 | (Continued)

First author	Year	Study design	Species (strain)	Tissue or cell type	Anatomical region	Biological sex	Age of subject	Primary interventions or assessment
Saeki Fernandes [147]	2018	Non-randomized experimental study	Rats (Wistar)	Articular cartilage	Femur	Female	Adult	OVX, E2, diabetes
Qin [148]	2013	Non-randomized experimental study	Rabbits (undefined strain)	Articular cartilage	Distal femur	Female	18.5 months	OVX, E2, electro-acupuncture
Luo [149]	2009	Non-randomized experimental study	Rats (Wistar)	Articutlar cartilage	Medial condyle of femur, tibial plateau	Female	3 months	OVX and HRT
Sniekers [150]	2009	Non-randomized experimental study	Mice (C57BL/6)	Articular cartilage	Knee	Female	6 months	ERα and ERβ KO
Silva [151]	2024	Non-randomized experimental study	Mice (CD-1)	Articular cartilage	Femoro-tibial joint	Female	Adult	OVX, DV and DSG
Sondergaard [152]	2007	Non-randomized experimental study	Rats (Sprague Dawley)	Articular cartilage	Knee	Female	8 months	OVX, E2, calcitonin, 5CNAC
Zaychenko [153]	2023	Non-randomized experimental study	Rats (Wistar)	Articular cartilage, subchondral bone, subchondral plate	Knee	Female	6–8 months	OVX, resveratrol
daSilva [154]	1993	Non-randomized experimental study	Mice (BALB/C) and Rats (Wistar)	Articular cartilage	Femoral head	Female	9–10 weeks	OVX
Christgau [155]	2004	Non-randomized experimental study	Rats (Sprague Dawley)	Articular cartilage	Knee	Female	6 months	SERM or E2 exposure after OVX
Harris [156]	2003	Non-randomized experimental study	Rats (Lewis)	Articular cartilage	Tarsal joint	Male and Female	12 weeks	OA and ERβ agonist (ERB-041)

(Continues)

TABLE 3 | (Continued)

First author	Year	Study design	Species (strain)	Tissue or cell type	Anatomical region	Biological sex	Age of subject	Primary interventions or assessment
Chang [157]	2014	Non-randomized experimental study	Rabbits (Japenese White)	Articular chondrocytes	Knee	Male and Female	12 weeks	E2 and testosterone
Hui [158]	2021	Non-randomized experimental study	Rabbits (New Zealand White)	Articular chondrocytes	Knee	Male	3 months	Androgen receptor overexpression
Kinney [159]	2005	Non-randomized experimental study	Human	Articular chondrocytes	Knee	Male and Female	16–39 years	17β-Estrogen
Rouge [160]	2023	Non-randomized experimental study	Horse	Osteochondral sections	Metacarpel	Male	11 and 18 months	OCX

Abbreviations: DHT; 5α-dihydrotestosterone, E2; 17β-estradiol, ER; estrogen receptor, HRT; hormone replacement therapy, IVD; intervertebral disc, KO; Knockout, OA; osteoarthritis, OCX; orchidectomy, OVX; ovariectomy, PTH; parathyroid hormone. SERM; selective estrogen receptor modulator.

and matrix degrading enzyme expression and activity (41/55). Clinical assessments such as IVD height and low back pain in patients were also reported (14/55). Studies focused on the nucleus pulposus consistently reported that estrogen attenuates apoptotic and pro-inflammatory signals induced by cytokines, ovariectomy (OVX), or disc injury [26, 36, 38, 41, 51, 57]. Additionally, estrogen exposure attenuated matrix degrading enzyme expression and increased proteoglycan and collagen content in cell cultures in a dose-dependent fashion [47]. It is important to note that many of these studies focused solely on NP cell culture models (14), and few studies investigated the effects of estrogen on the AF (3) or CEP (2). Of those that investigated the AF, primary investigations reported that estrogen prevented apoptotic signaling [36], increased cell proliferation [17], and recruited neutrophil precursors [39]. Studies focused on the role of estrogen in the CEP also observed decreased endplate mineralization [44] and increased proteoglycan content [47].

In vivo, estrogen deprivation through OVX consistently induced IVD degeneration across multiple animal models [18, 23, 44, 46, 48, 49, 52, 57, 58, 68, 69, 161]. This phenomenon is also reported in postmenopausal women [16, 19–21, 24, 27, 29, 40, 62, 67, 162]. Estrogen replacement mitigated many degenerative changes in animal models, including maintaining the redox balance by reducing reactive oxygen species [46] and reducing histopathological changes within IVDs [59]. IVD injury and estrogen deprivation by OVX were partially ameliorated by estrogen supplementation [60]. In women, estrogen replacement following menopause correlated with increased disc height [19, 20, 67], but these patients also reported increased low back pain [16]. Vertebral subchondral bone of mice was decreased following ovariectomy [48, 49].

The effects of testosterone on IVD biology are poorly investigated, limited to two studies. In 1969, a group investigated the effects of testosterone, estrogen, and parathyroid hormone on AF lamellae structure in a canine model [15]. They reported structural changes to the lamellar structure, including fragmentation and "loosening," with unknown biological consequences. The second study, in 2014, was a primary human cell culture experiment investigating the chondrogenic potential of testosterone in NP cells to facilitate the in vitro formation of tissue constructs [30]. Testosterone increased collagen type 2 and aggrecan gene expression in male IVD cells, and changes in gene expression were abolished by an aromatase inhibitor, preventing the conversion of testosterone into estrogen. A single case series study investigated the effects of testosterone in humans, where 60 patients (combination of male and female) with chronic lower back pain received testosterone and recombinant growth hormone injections locally to the site of pain [32]. The study reported a decrease in patients self-reported low back pain after 12 months.

3.3 | The Effect of Sex Hormones on the Temporal Mandibular Joint

3.3.1 | Study Design

Most articles identified for the TMJ were non-randomized experimental study designs (23); the remaining articles used randomized controlled trial (1), cohort (1), and cross-sectional

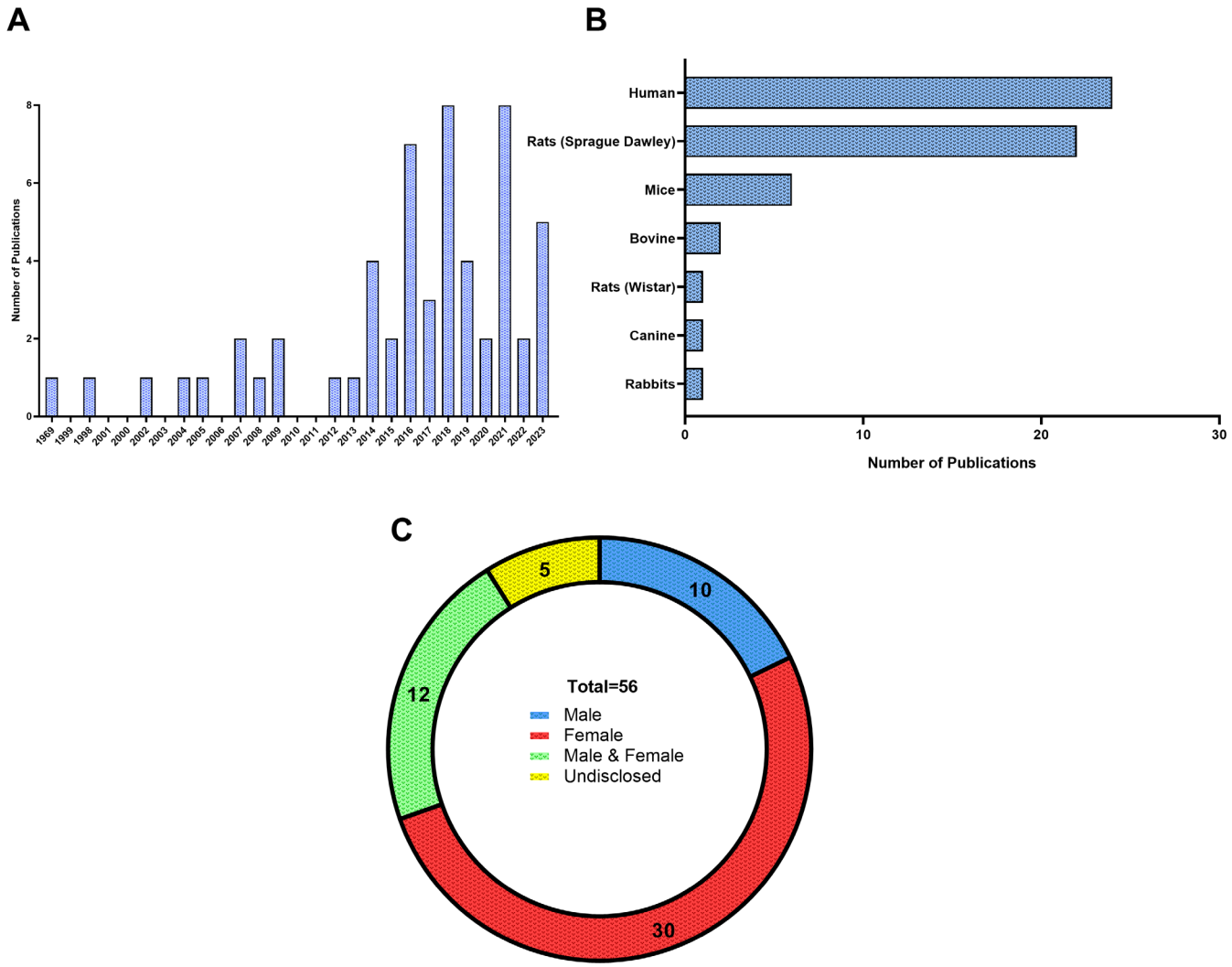

FIGURE 2 | Primary characteristics in IVD research investigating the role of sex hormones. (A) Publications identified in our search stratified by year of publication. (B) Model species used in the laboratory and/or clinic in each study. (C) Distribution of biological sexes investigated in IVD research related to sex hormones.

study (1) designs. Publications by year are reported for all studies identified (Figure 3A). The animal models used varied, with rats as the primary animal model used in studies (15), followed by mice (6), human (3), and baboon (2) models (Figure 3B).

3.3.2 | Distribution of Biological Sex, Age, and Hormones

Studies focused predominantly on female sex (69%), with two studies identified in our search examining males. Six studies used both male and female models (Figure 3C). Studies primarily focused on the effects of estrogen deprivation through ovariectomy (OVX) on the temporomandibular joint (54%) and estrogen receptor activation (35%). Three studies investigated the effects of testosterone on pain and collagen content following a gonadectomy. Human patients were examined in three studies ranging from adolescent to young adult (14–40 years of age) to identify associations between TMJ prevalence and genotypic variations.

3.3.3 | Key Findings: Temporomandibular Joint

In the late 1980s and early 2000s, estrogen receptors were identified within TMJ cells of the baboon [94] and rat [75]. Following this discovery, various animal models were used to investigate the effects of estrogen on TMJ biology, including changes induced by estrogen deprivation, receptor agonism, and receptor knockout [86, 89]. The effects of OVX or orchidectomy (OCX) on the integrity of the TMJ are still unclear. Some groups report increased cartilage thickness after sex hormone deprivation [71, 81], while another group showed decreased cartilage thickness [90]. Importantly, these studies differed in their use of model systems to evaluate TMJ cartilage thickness, with mouse models ranging from 21 days to 2 months of age and 2-month-old rat models. At baseline, there are sex-based differences in rat condylar

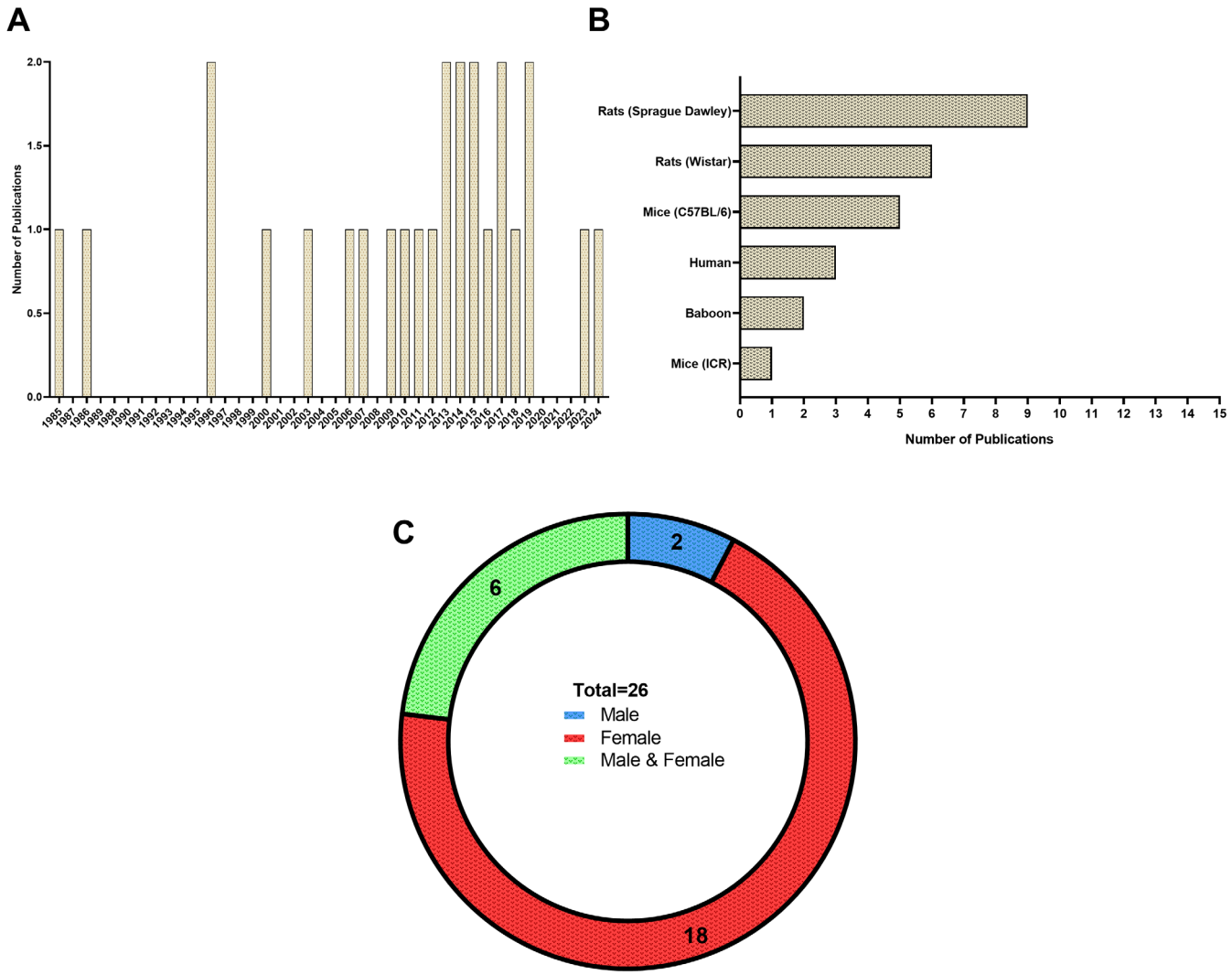

FIGURE 3 | Primary characteristics in TMJ research investigating the role of sex hormones. (A) Publications identified in our search stratified by year of publication. (B) Model species used in laboratory and/or clinic in each study. (C) Distribution of biological sexes investigated in TMJ research related to sex hormones.

cartilage within the TMJ. Male rats had higher collagen content than female animals, which was abrogated with castration in both sexes [74]. Estrogen receptor knockout has also been studied in rodent models of TMJ disease and suggests that loss of estrogen signaling has a detrimental effect on extracellular matrix production. For example, both male and female ERβ knockout mice had decreased collagen type X expression and subchondral bone integrity in the TMJ [125], similar to an ovariectomy study in rats which showed a reduction in collagen type II and X gene expression [72]. ERβ knockout mice were resistant to cartilage thickening observed in the ovariectomized mice [81] and ERα knockout negatively influenced TMJ maturation in mice, but not TMJ degeneration [163].

Interestingly, estradiol has pro-inflammatory effects within the TMJ. Castration increased cytokine levels in both sexes [83], and while testosterone supplementation mitigated pain [85] and TMJ damage, estradiol exacerbated TMJ damage in the presence of inflammation [87], TRPV1-mediated pain [78], and increased the expression of matrix metalloproteases [86].

3.4 | The Effect of Sex Hormones on Articular Cartilage and Chondrocytes

3.4.1 | Study Design

Study design for the assessment of articular cartilage was almost entirely non-randomized experimental studies (60), with few randomized controlled trials (3) and a single cross-sectional, case-control, and cohort study. Publications by year are reported for all studies identified (Figure 4A). Model systems primarily consisted of rat (20), human (14), rabbit (7), and mouse (6) subjects (Figure 4B).

3.4.2 | Distribution of Biological Sex, Age, and Hormones

Most studies investigated female animals (71%), while only two investigated males (3%), and several used both sexes (21%). Three studies did not disclose the sex of individuals (1 human, 1

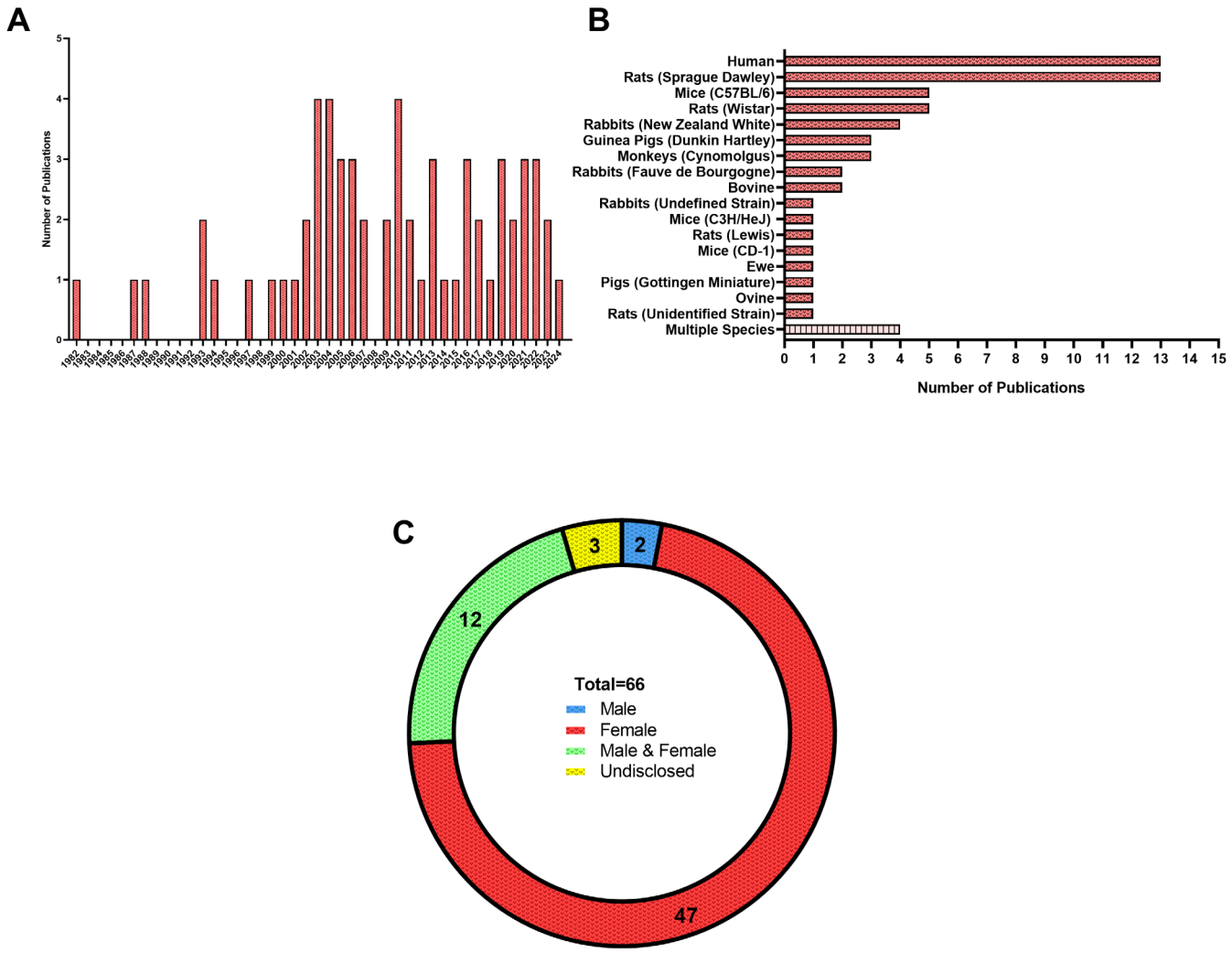

FIGURE 4 | Primary characteristics in articular cartilage research investigating the role of sex hormones. (A) Publications identified in our search stratified by year of publication. (B) Model species used in the laboratory and/or clinic in each study. (C) Distribution of biological sexes investigated in articular cartilage research related to sex hormones.

rabbit, 1 monkey, 5%) (Figure 4C). The most widely used interventions were OVX or OCX (37) to induce pathogenic features such as inflammation or osteoarthritis, or primary cell culture experimentation (16). Changes in osteoarthritis pathogenesis were then characterized following joint destabilization surgery alone or following treatment with various sex hormone agonists or hormone replacement therapy. Studies in humans examined age- and menopause-associated changes in osteoarthritis (> 50 years of age) and used primary cells isolated from tissue at the time of surgery, which enabled the use of tissues from a large range of ages (16–87 years of age). In vitro animal-based experiments used tissues and cells from neonatal to skeletally mature adult animals.

3.4.3 | Key Findings: Articular Cartilage

How sex hormones regulate joint health and the progression of osteoarthritis is a multifaceted research question, given that both involve interactions between cartilage, bone, and synovium and that osteoarthritis studies often focus on the management of patient-reported pain. Here we specifically focus on the effects of sex hormones on articular cartilage. Early cell culture studies showed estrogen receptor localization within rabbit and rat articular chondrocytes [98] and that rats expressed estrogen receptor α (ERα) in both biological sexes, which decreased after OVX [110]. This and subsequent studies characterized various effects of estrogen, including the attenuation of inflammatory gene expression in primary human chondrocytes isolated from the hip, knee, and ankle of OA patients [106, 113, 124], and increased miR-140 expression, which suppressed MMP-13 expression [118]. In primary chondrocyte cultures, estradiol reduced oxidative stress [108]. Estradiol and testosterone positively regulate chondrogenesis in male and female rabbit cells, with a larger effect from estrogen than testosterone in cells derived from both sexes [157].

Despite these positive findings in cell culture experiments, they contrast with findings on the effects of sex hormones on articular joints in vivo. Much of the variation in outcome is likely dependent on which animal model was used. In contrast to other reports suggesting negative effects of OVX on cartilage health, rabbits have increased cartilage thickness [96] and stiffness and decreased histopathological scores [111] with OVX, and high

doses of estradiol resulted in cartilage defects and fibrillations [101]. However, this response was dose-dependent; a low dose of estradiol did not result in changes to the knee cartilage [103]. In another study using primary rabbit chondrocytes, testosterone, dihydrotestosterone, and estradiol exposure all increased glycosaminoglycan production in an age-dependent manner (increased response with increased age) in male and female rabbits [102]. Androgen receptor overexpression was investigated in one study using rabbit models and showed regeneration of cartilage defects [158].

There is a consensus regarding the effects of depletion, replacement, or supplementation of sex hormones based on studies in the rat model. OVX induces osteoarthritis [114, 143], and both OVX and OCX decreased glycosaminoglycan content in articular cartilage [95]. In female rats, OVX-induced osteoarthritis was prevented with hormone replacement therapy [99]. Estrogen receptor beta agonist (ERβ-041) reduced histopathological joint scores, inflammation, and synovitis in rats [156]. It is noteworthy that few studies used male animals (15/62). Reports in murine models are consistent with those in rats; OVX in mice increased OA progression [123] and estradiol prevented cartilage damage following OVX [112]. Female mice treated with DHT and estradiol had reduced GAG loss in cartilage explant cultures [154].

Human studies investigating the effects of sex hormones on cartilage volume and the progression of osteoarthritis produced conflicting reports. For instance, cartilage degradation correlates positively with years elapsed since menopause [119], and estrogen replacement decreased cartilage turnover in postmenopausal women [131]. Tibial cartilage volume was also increased in patients who received estrogen replacement [127], and a reduction in matrix degrading enzyme expression [106], implying that estrogen signaling was important for maintaining cartilage health. However, there are also reports that estradiol exposure does not influence cartilage volume [130] or the progression of knee OA [145]. Furthermore, there were also reports that ERα was increased with age in OA patients [122], and that treatment of articular chondrocytes with low doses of estrogen increased chondrogenic markers, but high doses of estrogen decreased these markers [139]. Childbearing also increased the number of cartilage defects observed in knee cartilage [137]. Taken together, these studies show that the relationship between sex hormones and articular cartilage is multifaceted and depends on biological sex and model system.

4 | Discussion

4.1 | Summary of Evidence

The objective of this scoping review was to summarize the body of literature pertaining to the effects of sex hormones on joint tissues, particularly the IVD, TMJ, and articular cartilage. Our search results suggest that while this research is still in its infancy, sex hormones are important regulators of joint homeostasis, and removal of endogenous sex hormone production can underlie joint disease and certainly exacerbates age- and injury-associated joint pathologies [60, 92, 133, 155]. Importantly, the response of the animal models to sex hormone treatment, or removal, was conditional upon the sex, age, and the species being investigated. For instance, while there were positive implications within the IVD for disc height [67], and chondrogenesis [163], both indicators of IVD health, it should also be noted the incidence of low back pain was higher in groups receiving estrogen hormone replacement therapy [6]. Studies investigating the effects of testosterone and its derivatives on each of these joint tissues are extremely limited. Results from testosterone studies indicate positive molecular outcomes such as increased proteoglycan and collagen synthesis [30], and a reduction in patient-reported pain after testosterone treatment [32]. Importantly, we identified that while there are apparent sex differences in joint pathologies following treatment, some outcomes of testosterone or estrogen exposure were irrespective of biological sex [74, 95, 102], including a clinical case series following testosterone injections in men and women [32]. These reported differences require further investigation so that laboratory models can better simulate clinical outcomes. Given the presence of sex hormone receptors on cells of multiple joint tissues in both sexes, it is also likely that there are independent and coactivation of androgen and estrogen receptors, which impact joint tissues.

A consistent finding across studies examining the various joint tissues investigated was the role of sex hormones in modulating the inflammatory response. Aberrant inflammatory signaling can promote disease pathology such as IVD degeneration [164, 165], TMJ disease, and osteoarthritis [166, 167]. Few studies investigated the effects of both testosterone and estrogen within their model systems, and this is a limitation to drawing strong conclusions, as the enzyme aromatase can actively convert testosterone to estrogen, and therefore the effects of testosterone could be confounded by those of estrogen. The relationship between the conversion of testosterone to estrogen could be addressed in these models using non-aromatizable testosterone (DHT), or aromatase inhibitors, as previously described [30].

Important to note, IVD height, an indicator of IVD health, was assessed in women receiving hormone replacement therapy, as was the rate of height loss between men and women with aging. Disc height correlated negatively with the onset of menopause, whereas men had increased disc degeneration at a younger age, perhaps due to differences in injury rates between men and women [40, 168]. Importantly, disc height was increased in women receiving hormone replacement [19, 67]. There were no studies that assessed clinically the effects of sex hormones on the temporomandibular joint; however, similar to the IVD, articular cartilage volume is negatively correlated with menopause [119], and hormone replacement therapy increased articular cartilage volume in post-menopausal women [131]. Of note, we did not identify any clinical studies investigating testosterone replacement therapy and age-associated changes in disc height, temporomandibular joint disease, or articular cartilage volume. Although aging results in the loss of circulating testosterone at a much different rate in men than women, approximately 1% per year after 30 years of age [169], there still remains an important gap in our research knowledge regarding how sex hormones influence joint health in the aging male. Importantly, testosterone and estrogen use is not limited to male and female biological sex, respectively, and can be used by both sexes in the context of sport [170–172] or treatment of gender dysphoria [173, 174]. Given an increasing population of individuals who

seek hormone-based therapy for sexual transitioning each year [173], it is imperative that research explores the effects of these types of hormone regimes on joint homeostasis and long-term health in these individuals.

4.2 | Limitations Within the Field

There are some limitations impacting the data acquired throughout this search that we feel are important to bear in mind when interpreting the results of this review. First, the retrieval of human samples are often limited to those being excised during surgery or post-mortem; and confounding factors such as surgery- or necrosis-induced degeneration are a consideration that may impact findings. Due to the degenerative features or advanced age of these tissues, the effects of sex hormones on joint homeostasis are poorly understood, limiting analysis to their influence on the degenerative phenotype. Although randomized experimental trials were limited in human subjects, and cross-sectional, cohort, or longitudinal studies are limited by sampling bias, they remained powerful assessments for determining sex-based differences in aging and the effects of hormone replacement. Animal models are also limited, as almost all laboratory animals do not enter menopause with age [175, 176]. This necessitates researchers to use castration models to block sex hormone synthesis to mimic the effects of menopause, often requiring surgery or complex medication that could interfere with the progression of disease.

5 | Conclusion

In summary, we found that reports show the effects of sex hormones on the IVD, TMJ, and articular cartilage are sex-, species-, age-, and tissue-dependent. Overall, the role of estrogen may not be entirely positive as predicted by pre-clinical animal models, as commonly believed. While there are positive implications in clinical assessments such as IVD height and cartilage production, patients may also report increased pain. Many reports, particularly focused on the TMJ and articular cartilage, are inconsistent. Studies on the effects of testosterone on joint tissues are limited, and although there are beneficial implications for IVD, TMJ, and articular cartilage biology, further studies are warranted to understand the biology underlying joint health and to develop therapeutics for patients suffering from joint pathologies.

Conflicts of Interest

The authors declare no conflicts of interest.

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