In 2004, the American Academy of Orthopaedic Surgeons’ (AAOS) Women’s Health Issues Committee, the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health (NIH), and the NIH Office of Research on Women’s Health co-sponsored the workshop *Does Sex Matter in Musculoskeletal Health? The Influence of Sex and Gender on Musculoskeletal Health* to explore how male and female biologic and physiologic characteristics affect musculoskeletal health. The program underscored the fact that sexual dimorphism occurs at the genetic, cellular, and tissue levels and drives the biomechanics of orthopaedic tissues, as well as differences in injury mechanism, pain sensation, drug handling and healing responses. Similarly, the workshop report emphasized the need for greater awareness of sex differences in the design of in vitro and preclinical animal studies, the impact that sex differences have on health and treatment of musculoskeletal conditions, and the need for appropriately powered studies to be able to identify sex differences in the human population.

2014 marked the 10th anniversary of the original workshop. Although the first workshop influenced the thinking of many basic scientists, progress in translating the 2004 findings into improved clinical practice has been disappointing, especially with respect to the impact of these findings for different stages of the life cycle (a particularly important issue for women). In response, the original workshop leadership team partnered with the Association of Bone and Joint Surgeons (ABJS) (publishers of Clinical Orthopaedics and Related Research [CORR]), the Orthopaedic Research Society (ORS), the Center for Musculoskeletal Health at the University of California, Davis (CMH-UCD), the Society for Women’s Health Research, the National Institutes of Health, as well as the current and past chairs of the AAOS Women’s Health Issues Advisory Board to sponsor the 2014 symposium, *Musculoskeletal Differences Throughout the Lifespan*.

The planning committee wishes to thank the Association of Bone and Joint Surgeons. Original research presented at the symposium will be published as a special section in *Clinical Orthopaedics and Related Research* in the near future.
Influence of Genetics and Anatomical Differences

Sexually Dimorphic Differences in the Incidence of Musculoskeletal Conditions and Injuries

Changing Perspective: Anatomic and Genetic Contributions to Osteoarthritis (OA)

Developmental Dysplasia of the Hip (DDH) Differs from Adolescent/Adult Acetabular Dysplasia

- Acetabular Dysplasia is 48% of THR
- BUT no association between parameters for acetabular dysplasia and hip OA in males

DDH Characteristics

- Female
- Left
- Breech

Adolescent/Adult Acetabular Dysplasia

- Male
- Bilateral
- Similar to Wynn-Davies late diagnosis group
  - Closer sex ratio
  - More bilateral involvement
  - Hip morphology is more similar between the two sides in the non-DDH group (Okano, et al Orthop Science 2008:13:401-404)
  - Suggests that non-DDH acetabular dysplasia is a generalized malformation of the hemipelvis

Emerging Role of Femoroacetabular Impingement (FAI)

- FAI is the most common mechanism for the development of early osteoarthritis in the nondysplastic hip
- Anatomic abnormalities of proximal femur and/or acetabulum
- Repetitive collision with dynamic hip motion that damage the cartilage and labrum
- Regional loading of femoral head-neck junction with acetabular rim and abnormal kinematics can precipitate early osteoarthritic changes

Sex Differences in FAI

- Overall prevalence unknown ~ 20% cam lesions in males, 9% females (Gosvig, 2010)
- Beaule et al: cam-type FAI in males > females
- 79% who had an elevated alpha angle were male; 21% female
- 24.7% (twenty-two) of eighty-nine men having cam morphology compared with only 5.4% (six) of 111 women
- Differences in femoral antetorsion
- Mean values differed between 17.8° ± 8.9° and 22.7° ± 10.7° in women and 15.3° ± 8.0° and 21.4° ± 9.7° in men (Decker et al)
- Males demonstrated significantly less acetabular anteversion than females in every section. The global version was also significantly different between males and females (16° ± 7° and 19° ± 8° respectively, P<0.001). (Sekiya, Bedi et al)

Explaining Sexual Dimorphism in Common Musculoskeletal Disorders: The Carter Effect

The Carter Effect notes that when there is a lack of a specific disease-causing gene AND sex discrepancy in the absence of sex-linked inheritance, that the trait demonstrates a polygenic inheritance model with a dimorphic sex threshold for the affected phenotype. (Carter CO, Evans RA. J Med Genet. 1969:6:243-54)

Clubfoot

- 2.5-4 times more common in males than females
- Thus, females require a greater number of, or more potent, susceptibility genes than males to inherit clubfoot
- Females would be predicted to have a higher rate of transmission of the affected phenotype to their children (not yet demonstrated)

Adolescent Idiopathic Scoliosis (AIS)

- AIS 10x more common in females than males
- No single gene has been found
- Genome-wide association studies and other linkage analyses have shown evidence for the involvement of numerous different areas in the human genome
- These data also support the evidence of the Carter effect in AIS
- Males, who are less commonly affected with AIS, appeared to require a greater genetic load to become affected
- Males are more likely to transmit the disorder to their offspring (M:F 3.28 times more likely to transmit AIS to their children (p < 0.001) Kruse et al JIBS 54:16. 1485-1492. (2012)

Genetic Contributions to Bone Fragility: The Role of Sex

- Why are females at greater risk than males?
  - Hormonal changes during perimenopause
  - Lower peak BMD
  - Structure/morphology differences of hip, body size
  - Physiological demands of pregnancy/lactation

- Why are some females at higher risk than others?
  - Timing of menarche, perimenopause
  - Lower peak BMD
  - Structure/morphology differences of hip, body size
  - Physiological demands of pregnancy/lactation
  - Physical activity variations

- Why are some males at high risk?
  - Lower peak BMD
  - Structure/morphology differences of hip, body size
  - Hormonal variation
  - Physical activity variations

- The Unmet Challenge
  - Determine which genes or pathways play a role in risk
  - Finding these genes and understanding their mechanism of action will vastly improve our understanding of sources of variation in bone fragility.
Musculoskeletal Development and Peak Bone Mass

Sexual Dimorphism in Bone Growth

Women build bone that is fundamentally different from men.
- Female bone has lower cortical area than men – even lower than expected for having more slender bones
- Differences in material properties between male and female bone do NOT compensate for this difference
- Thus, women build bone that is weaker than that of men from the outset

Sexual dimorphism in peak bone mass is related to the cells’ response to hormones, muscle activity, and other factors affecting rates of growth.

Sex differences in DXA-based measures of skeletal growth—Results from the Bone Mineral Density in Childhood Study:

Magnitude of bone accretion by pubertal stages differs among males and females:
- Bone accretion is very stable in Tanner stages 1-2
- Bone accretion continues in Tanner stage 5

Effects of growth and body composition vary according to pubertal status:
- Increments in height have a greater effect later in puberty compared to earlier pubertal stages
- Lean mass increments are especially important in mid-puberty, and remain higher in males than females in later puberty
- Fat mass accretion has a positive effect on TBLH BMC accretion in older girls and negative effects on spine BMC accretion in boys and girls

Sexual Dimorphism During Puberty

Data based on the Fels longitudinal study (1929-present)
- Female vs. male metacarpal shows:
  - The average age of onset of growth is 11.5 years (f) vs. 13.9 years (m)
  - The peak velocity of growth is at ~11.5 years (f) vs. 14 yrs (m)
  - The cessation of growth occurs at 15 years (f) vs. 17 years (m)
- Similar changes in bone diameter – i.e. there is earlier maturation (2 years) in girls than boys.
- Males have larger periosteal envelopes during puberty and greater endocortical envelopes when they mature
- Timing of menarche has impact on bone strength: later menarche = stronger bones

Sexual Dimorphism in Hormonal Action

- Estrogens have distinct effects in males and females
- Estrogen stimulates periosteal expansion via estrogen receptor α in males.
- Estrogen inhibits periosteal apposition, endocortical resorption and chondrocyte remodeling, via estrogen receptor α in females
- Androgens affect bone formation in males and females: in males, androgen acts on osteoblasts and osteocytes via the androgen receptor to increase trabecular bone formation
- Progesterone, via its two receptors that are expressed in bone and chondrocytes, also affects bone formation
- In mice the global knockout of the progesterone receptor caused increased bone and was not affected by estrogen deficiency. A similar effect was achieved by use of RU486, a progesterone receptor inhibitor

Sexual Dimorphism in Skeletal Muscle Development

- Muscle strength in males > females; endurance is greater in females. Does this relate to peak bone mass?
- Muscle fiber area is increased in males
- Specific tension (force/area) is equivalent in males and females and neural motor units are equivalent in males and females
- Muscle fiber types DIFFER in males and females:
  - Females have more type 1 fibers (oxidative, slow twitch, endurance) while males have more type 2A (oxidative-intermediate) and 2X (fast twitch, high-force quickly, glycolytic—short duration); women have higher capillary density
- Stem cells differ in distribution; males have more satellite cells and a slightly higher number of myonuclei. Satellite cells are the primary stem cells for growth and repair

Can Exercise Alter Peak Bone Mass?

- Unfortunately, studies do not always show a greater increase in bone mass or size in children assigned to exercise compared to no exercise.
- A higher percent of studies found changes in the pre- & early-pubertal stages compared to post-pubertal. However, very few trials have been done in post-pubertal children.
- Other factors (baseline BMI, activity levels, dietary calcium intake) may influence the bone response to loading.
**The Influence of Inflammation**

Females are more likely to develop autoimmune diseases than males.

### Sex Ratio of Various Rheumatic Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Female:Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sjögren's Syndrome</td>
<td>9:1</td>
</tr>
<tr>
<td>Systemic Lupus Erythematos</td>
<td>7:1</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>3:1</td>
</tr>
<tr>
<td>Systemic Sclerosis</td>
<td>3:1</td>
</tr>
<tr>
<td>Psoriatic Arthritis</td>
<td>1:1</td>
</tr>
<tr>
<td>Ankylosing Spondylitis</td>
<td>1:3</td>
</tr>
</tbody>
</table>

### Epidemiology of Rheumatoid Arthritis

- **The prevalence of RA is about 1-2% US population**
  - 4-5 times higher in females than males before age 50
  - 2x as high in females and males after the age of 70 years
  - Etiology of sex difference is not clear
- **Risk factors for RA include genetic (47%), non-genetic and environmental <50%**
- **While both males and females respond to standard treatments for RA, males report more improvement than females in both disease activity and patient centered outcomes**

### Ankylosing Spondylitis (AS)

- **Female:Male Ratio is 1:3**
- AS is diagnosed later in females than in males
- Fewer, and later, radiographic changes in females
- **Clinical Criteria:**
  - Low back pain and stiffness for >3 months, which improves with exercise but is not relieved by rest
  - Limitation of motion of the lumbar spine in both sagittal and frontal planes
  - Limitation of chest expansion relative to normal values for age and sex
- **Radiographic Criterion:**
  - Sacroiliitis (grade ≥2 bilaterally or grade 3–4 unilaterally)
- **Recent stratification of AS types**:
  - Ankylosing Spondylitis (AS) vs. Non-radiographic Axial Spondylitis (nr-axSpA)

### Systemic Lupus Erythematosus (SLE)

- Differences in immunologic response (male vs female)
- Exogenous sex hormone administration
  - *In vivo* studies of humans and animals show little effect on response to vaccine or infection
  - OCPs or ERT or pregnancy does not worsen or increase risk of lupus
- Serum Levels at onset of disease: No changes in sex hormones
- **New Perspective**: Sex “biased” genes are influenced by X Chromosome Dose Effect
  - Hypothesis: Number of X chromosomes is a risk factor for autoimmune disease, not phenotypic sex

### Sex Bias in Autoimmune Disease

Only a few sex specific genetic loci identified so far; none explains sex bias and there is no evidence of X-linked effect. But, For SLE and Sjögren’s, the X chromosome dose effect, not phenotypic sex, accounts for the 10-fold increased risk.

#### 47,XXX in Other Diseases:

- **Sex biased disease**:
  - Rheumatoid arthritis
  - Primary biliary cirrhosis
- **Sex neutral disease**:
  - Sarcoidosis
  - Polyangitis with granulomatosis

### Additional Sources

- Chang CM, Chang CC, Chue CH, Chu SJ, Chang ML. Hormonal profiles and immunological studies of male lupus in Taiwan. Clin Rheumatol 18:258-64, 1999

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**Example: SLE and Sjögren’s in patients with 47,XXX**

**Comparison of AS and nr-axSpA**

- *In vivo* studies of humans and animals show little effect on response to vaccine or infection
- OCPs or ERT or pregnancy does not worsen or increase risk of lupus
- Serum Levels at onset of disease: No changes in sex hormones
- After SLE begins: No different than males w/other chronic diseases
- **New Perspective**: Sex “biased” genes are influenced by X Chromosome Dose Effect
  - Hypothesis: Number of X chromosomes is a risk factor for autoimmune disease, not phenotypic sex

**Sex Differences in early AxSpA**

- *In vivo* studies of humans and animals show little effect on response to vaccine or infection
- OCPs or ERT or pregnancy does not worsen or increase risk of lupus
- Serum Levels at onset of disease: No changes in sex hormones
- After SLE begins: No different than males w/other chronic diseases
- **New Perspective**: Sex “biased” genes are influenced by X Chromosome Dose Effect
  - Hypothesis: Number of X chromosomes is a risk factor for autoimmune disease, not phenotypic sex

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**47,XXX in Other Diseases:**

- Rheumatoid arthritis
- Primary biliary cirrhosis
- Sarcoidosis
- Polyangitis with granulomatosis

**Sjögren’s** and Sex Bias in Autoimmune Disease: Increased 47,XXX in Systemic lupus erythematosus and Sjögren’s syndrome, in preparation
Osteoarthritis (OA) is the fastest growing major medical condition worldwide. Osteoarthritis of the knee affects 250 million people worldwide and the rate of total knee arthroplasty has doubled in the last decade. There are approximately 3 million women and 1.7 million men who have had total knee arthroplasty living in the United States.

Contributors to Sex Differences in Knee OA
- Females lose knee articular cartilage at a faster rate than males with age
- Obesity and hand OA are stronger risk factors for knee OA in females than in males
- History of knee injury is a stronger risk factor for males
- Quadriceps weakness raises the risk of knee OA by increasing the load transmitted to the knee joint; females are more likely to suffer from quadriceps weakness

The Role of Hormonal Influences on the Development of Knee OA is Not Fully Understood
- Female human articular chondrocytes may function better when estrogen is available
- Male human articular chondrocytes are more responsive to vitamin D metabolites than female cells
- Vitamin D receptors and mRNA for inflammatory cytokines are differentially expressed in degenerated cartilage in a sex-specific fashion
- Subchondral bone osteoblasts exhibit sex specific responses to estrogen

Osteoarthritis is Joint Failure: Disease Process Involving the Entire Joint
- Cartilage fibrillation, degradation, loss
- Osteophytes
- Subchondral bone cysts
- Bone attrition
- Synovitis
- Meniscal degeneration
- Weakness of periarticular muscles

Response to Therapy
After surgery, function improves for both genders but women do not reach the same functional level as men.

Functional Outcomes: Gender Differences in Knee Society Scores

<table>
<thead>
<tr>
<th></th>
<th>Pre-Op</th>
<th>Post-Op</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritter MA et al. J. Arthroplasty 2008</td>
<td>Men</td>
<td>45.8</td>
<td>85.8</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>42.4</td>
<td>77.5</td>
</tr>
<tr>
<td>MacDonald SJ et al. Clin Orthop Relat Res. 2008</td>
<td>Men</td>
<td>48.7</td>
<td>70.8</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>41.3</td>
<td>59.9</td>
</tr>
</tbody>
</table>

Final function for women is not as good. They never catch up.

The lacunar-cannalicular network becomes disrupted with aging:

- Much work remains to establish sex-specific differences in mechanosensitivity
- Bone mineral content (BMC) correlates strongly with fat-free mass
- Males and females show similar relationships between BMC and fat-free mass
- Females show a decrease in fat-free mass, but not fat-mass, with aging
- Fewer studies on these relationships for males
- Sex-hormone suppression and loss of reproductive function begins 1-2 decades earlier in females compared to males

- Female baboons show a greater femur strength:body mass ratio compared to males
- Principal components analysis applied to the baboon proximal femur identified 6 PCA modes that differed by sex, 6 modes that differed by age for females, 5 modes that differed by age for males

**Bone**

**Muscle**

- **Sex disparities in study design**
  - 5 times as many males enrolled in muscle studies compared to females
  - Sex differences in muscle fatigue depends on the task involved
  - Females have slower and more fatigue resistant muscles compared to males
  - Males have muscles that respond faster than females, but fatigue more over time

- **Sex differences in older adults**
  - Older females have reduced strength and power at baseline compared to males
  - Females show a loss in fatigability
  - Sex differences in muscle function reduces with aging as females may become more fatigable

- **Increased cognitive demand reduces the time to task-failure**
  - Females become more fatigable compared to men with the added cognitive demand
**Aging: Changes at the Cellular Level**

**Implant Design**

For young animals, implant design may not matter. But for older animals, implants with micro-textured hydrophilic surfaces lead to more bone to implant contact and greater blood vessel formation.

*P. Olivaras-Navarrete, A. Flavell et al., J Bone Min Res, 2012*

**Stem Cell Research**

**The Effect of Sex**

- Sexual dimorphism (by donor) has been noted in multiple stem cell types including endothelial progenitor cells, bone marrow stem cells and osteoprogenitor cells, adipose stem cells, and neural stem cells.
  - Adipose-derived stromal cells harvested from female mice differentiate more efficiently into adipocytes than those from male mice (Ogawa R. et al., Biochem Biophys Res Commun. 2004 Jun 25;319(2):51-7).
  - Male and female osteoprogenitor cells respond similarly to titanium implant surfaces, but their response to estrogen, DHT and 1α,25(OH)2D3 differs in a surface dependent manner (Olivares-Navarrete R et al. Biol Sex Differ 1:4, 2010).
  - Regulation of osteoblast differentiation by acid-etched and/or grit-blasted titanium substrate topography is enhanced by 1α,25(OH)2D3 in a sex-dependent manner (Olivares-Navarrete R et al. Biomed Res Int, 2014, in press).
  - Female muscle derived stem cells (MDSCs) regenerate skeletal muscle in a more effective manner than their male counterparts (Deepak MA et al. Cell Res Elaboration Gene Exp 15:177-88, 2008).
  - Better cell survival
  - Better resistance to stress
  - Better muscle regeneration
  - Produce less fibrosis
  - BUT M-MDSCs repair articular cartilage more efficiently than F-MDSCs (Matsumoto T et al. Arthritis Rheum 58:3809-19, 2008)

**The Effect of Aging**

- Sexual dimorphism Neural and male germline stem cells from 2 yr-old mice show reduction in number and proliferation capacity (Hu BY et al. Stem Cells 2000).
- Hematopoietic stem cell number is preserved, but function is lost (Conboy IM et al. Dev Cell, 2002).
- Bone marrow-derived MSCs lose proliferation and differentiation potential and increase in senescence and decreased bone formation in vivo (Settle, S et al. Aging Res Rev, 2006).
- Similarly aged muscle derived stem cells demonstrate reduction in their reproduction and proliferation capacity.
- And, in mouse models, younger cells are able to perform a “rescue mission” but the mechanism is unknown.

**Sex Differences in Bone Loss and Fracture Rate**

**Differences in Hormone Status**

- Fundamental differences in changes in sex steroids with aging contribute to different patterns of bone loss in women vs men.
- Abrupt decrease in total and bioavailable estrogen levels in women at the time of menopause.
- More gradual decreases in serum bioavailable testosterone and estrogen levels in men starting at age 50-60 years.
- Marked increase in men in serum SHBG levels starting at age 50-60 years.

**Bone Quality Declines with Age, Independent of DXA Measures**

(Orwoll et al. JAMA 291:2555, 2004)

**Trabecular Bone**

- Compared to young women, young men began adult life with indices of trabecular structure that predict stronger bones and a greater resistance to fracture (higher BV/TV, TbTh).
- Age-related bone loss in men is due principally to trabecular thinning whereas women have marked reductions in trabecular number; the latter is particularly detrimental to bone strength.
- Early substantial trabecular bone loss in both sexes during sex steroid sufficiency indicates that current paradigms on the pathogenesis of osteoporosis are incomplete.

**Cortical Bone**

- Onset of substantial cortical bone loss in middle life in women and after age 70 in men occurs concomitantly with documented menopausal and late-life decreases in sex steroids in each sex, respectively.
- Older women and men have significantly worse measures of cortical microstructure that are independent of DXA aBMD:
  - Increased cortical porosity
  - Increased cortical pore volume
  - Increased cortical pore diameter
  - Increased cortical pore diameter distribution
- The DXA-independent effect of age on “bone quality” appears to be due to increases in cortical porosity in both sexes.