

## Analysis of Potential Effects of Estrogen on Ligament Stiffness and Resulting Injury Prediction Metrics

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### I. INTRODUCTION

Females have higher injury and fatality risk compared to males in automotive crashes [1-2]. Recent field data analyses have shown these sex discrepancies are greater for younger females (pre-menopause) than older females (post-menopausal) when compared to age-matched males [2-3]. Most injury data collected on pre-menopausal females come from female athletes and have clearly demonstrated that risks of some injuries vary with the menstrual cycle [4]. Additionally, joint laxity and resulting range of motion throughout the body varies across the menstrual cycle for females and becomes more similar to males post-menopause [5-6]. These studies suggest sex hormones could have an effect on joint response and injury tolerance, which could help explain why injury discrepancies between the sexes are more predominant in vehicle crashes at younger ages.

Furthermore, endocrinology research has found that sex hormones affect collagen by regulating its production, denaturing, and turnover rate [7]. As collagen is the basis of many biological tissues, it follows that structural changes in collagen concentration or organisation at nano- or micro-scale could result in changes in the macro-scale material response of a tissue. This hormonal regulation is complicated; hormone changes have variable delays in tissue response, and different combinations of hormones can change collagen response [8-9]. However, one hormone effect is consistent: ligament laxity increases with increasing  $17\beta$ -estradiol [10-11], which is the highest circulating form of estrogen in non-pregnant females. While trends in ligament stiffness from estrogen are known, it is unknown if these stiffness changes affect injury prediction metrics.

Therefore, this study aims to perform a sensitivity study on ligament stiffness (evaluating stiffness ranges consistent with estrogen effects defined from the literature), and to determine if these variations affect injury prediction metrics in finite element (FE) models. The sensitivity study will use a modified Global Human Body Models Consortium (GHMBC) mid-size male lower extremity (LEX) model in ankle dorsiflexion loading [12].

### II. METHODS

In order to assess estrogen effects on injury prediction metrics, and not confound them with sex differences in bony geometry, it was necessary to use a single LEX geometry. A modified GHMBC mid-size male model with updated foot and ankle male ligament material properties was chosen, as it was shown to have improved male biofidelity over the original GHMBC model [12]. The proximal tibia was fixed, and a pre-simulation applied 100 N axial load was performed to maintain ankle joint bony contact. A rigid plate translated in the z-direction at 6.9 m/s, contacted the ball of the foot and moved a further 17 cm, generating ankle dorsiflexion. This load condition was chosen as it was evaluated against male post-mortem human subject (PMHS) data in the initial validation of the modified GHMBC LEX model, and it matched a severe but realistic vehicle intrusion [12-13].

Because there is very little ligament material property data on pre-menopausal females, the choice of ligament stiffness ranges to vary came from two studies. A study of failure properties of the ACL from young (17–50 years) PMHS found average female elastic modulus was 20% lower than average male elastic modulus [11]. The hormonal state of each donor at death was unknown. Therefore, the current study assumes that the material properties from the female PMHS tested in [11] represent an average cycle stiffness of a ligament for a pre-menopausal female. All foot and ankle ligament stiffness curves from the modified male GHMBC were decreased by 20% to represent the “average pre-menopausal female”. Only one study has quantified soft tissue stiffness change throughout the menstrual cycle: fibroglandular tissue in the breast doubled in stiffness between maximum and minimum estrogen in normally cycling female volunteers [14]. While fibroglandular tissue is not technically a ligament, it is a collagenous connective tissue that supports the structure of the breast, similar to the collagen composition and function of ligament. Therefore, changes in ligament stiffness throughout the menstrual cycle were modeled by using the stiffness response that represented the “average

pre-menopausal female”, and further scaling them by adding or subtracting 33% of the stiffness response. This resulted in the maximum female ligament stiffness (minimum estrogen state) being twice as high as the minimum stiffness (maximum estrogen state), with the “average” female stiffness in the middle. Ligament failure metrics defined in the original modified GHBM mid-size male remained unchanged for this study.

Ligament failure location and timing, and the maximum first principal strain from a single element for all bones was output for each of the simulations. Dorsiflexion angle at ligament failure and peak strain in bones were also calculated. Finally, six degree-of-freedom bony kinematics were also compared across all simulations.

### III. INITIAL FINDINGS

Initial findings show negligible differences between the bony kinematics of the simulations representing four estrogen states and ligament failure timing and was comparable. However, strain distribution in the talus and calcaneus differed. Three neighbouring elements exceeding strain threshold was defined as failure, and failure time and dorsiflexion angle for the talus and calcaneus are reported in Table I. Results show increasing ligament stiffness led to earlier failure of the calcaneus, and decreased likelihood of talus fracture. These results suggest changes in ligament stiffness change strain distribution in ankle bones for dorsiflexion loading.

TABLE I

SIMULATION RESULTS OF INJURY METRICS AND ANGLE OF DORSIFLEXION AT WHICH THEY OCCURRED ARE SHOWN FOR FOUR DIFFERENT ESTROGEN STATES (LEFT). DIFFERENCE IN STRAIN DISTRIBUTION IN CALCANEUS IS ALSO SHOWN FOR MINIMUM AND MAXIMUM ESTROGEN STATES (RIGHT)

Ankle Ligament E Values (Representative Estrogen State)	Calcaneus failure time (° dors)	Talus failure time (° dors)	Calcaneus 1 <sup>st</sup> Principal Strain
GHBM default foot and ankle Es (male ♂)	11.8 ms (36.8°)	No failure	maximum estrogen 6.000e-02 5.220e-02 4.440e-02 3.660e-02 2.880e-02 2.100e-02 1.320e-02 5.400e-03 -2.400e-03 -1.020e-02 -1.800e-02
Male Es – 20% of Male Es [11] (pre-menopausal female average ♀)	7.9 ms (25.3°)	24.2 ms (73.1°)	
Avg female Es -33% Avg female Es [12] (maximum estrogen volume for ♀)	6.6 ms (21.2°)	21.7 ms (67.3°)	
Avg female Es +33% Avg female Es [12] (minimum estrogen volume for ♀)	14.4 ms (46.1°)	No failure	

### IV. DISCUSSION

This study demonstrates that changes in ligament material properties due to estrogen effects have the potential to change the injury prediction metrics, primarily through changes in strain distribution. It should be noted that because so few studies have quantified material properties for young females, it is unknown if the stiffness ranges evaluated in this study are consistent throughout the body, or if they represent an over- or underestimate of the average change in ligament stiffness with hormonal state. Despite this limitation, initial results suggest that estrogen effects result in greater variability in ligament stiffness in the female population, and these variations can subsequently affect load distribution and injury location. Therefore, there is a need for additional quantification of female tissue material properties to better capture variability in injury risk throughout the entire population. By correlating stiffness to changes in serum hormone volumes, the field of automotive injury may gain more insight as to what is contributing to sex discrepancies in injury for younger occupants, and possibly determine if there is a hormonal state at which females are most vulnerable to injury, which should be evaluated when designing injury countermeasures and safety restraints.

### V. REFERENCES

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