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Age-dependent mathematical models of ligaments and tendons

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ABSTRACT

Understanding the internal structure and the underlying physical mechanisms governing the mechanical properties of ligaments and tendons, particularly the elastic modulus, across different stages of life is critical for enhancing tissue strength during growth, maturation, and aging. This knowledge is essential not only for preventing tissue failure in older adults but also for advancing the development of biomaterials that can substitute or augment ligament and tendon function across all age groups. Despite the significance of this area, a comprehensive, mechanistic understanding of the relationship between structural changes and mechanical properties over time remains largely unexplored. To date, there is a lack of detailed studies that elucidate the physical mechanisms involved in these age-related changes. The absence of such mechanistic insights highlights a significant gap in the literature, necessitating further investigation. Therefore, this research delves into the age-dependent structural and mechanical property changes in ligaments and tendons, emphasizing both growth and mature phases. Utilizing a comprehensive approach, we have developed new mathematical models that directly correlate the growth of collagen in fibrils with the increasing elastic modulus in the fibers of ligaments and tendons over time. By integrating experimental data from mouse tail tendons in published work and conducting simulations, we have observed that the cross-sectional area of collagen in fibrils and the elastic modulus of a collagen fiber increase rapidly during the growth phase and stabilize during the mature phase. Our proposed models effectively describe the trends in collagen growth and the elastic modulus of fibers in ligaments and tendons over different ages, exhibiting consistency with experimental data. Through detailed analysis, we elucidate the mechanistic relationship between collagen growth and the elastic modulus of fibers as they age. This comprehensive approach significantly enhances our understanding of the age-related structural and mechanical property changes in connective tissues, providing a robust framework for future investigations.

Keywords: Age-dependent, Mathematical models, Structural changes, Ligaments, Tendons

INTRODUCTION

The mechanical properties of ligaments and tendons, particularly their elastic modulus, play a crucial role in maintaining tissue integrity and function across the human lifespan. These properties are intricately linked to the internal structure and the underlying physical mechanisms that govern them, which evolve significantly with age. Understanding these age-related structural and mechanical changes is essential not only for improving tissue strength during periods of growth and maturation but also for mitigating the risk of tissue degeneration and failure in aging populations.

Research on improving the quality of ligament and tendon substitutes has been extensively published and continues to attract significant interest [1, 2]. To create age-appropriate and effective scaffolds, it is crucial to understand the age-related structural and mechanical property changes in connective tissues.

One critical age-related mechanical property affecting the behavior of ligaments and tendons is the elastic modulus. Understanding the structural origins that influence the elastic modulus over time is essential for describing mechanical or viscoelastic behaviors, such as tensile strength, creep, relaxation, and hysteresis, which are vital for design and prediction. This study focuses on the structural changes related to variations in the elastic modulus of fibers in ligaments and tendons over different ages.

Despite various age-related modeling and experimental approaches to understanding the physiological and mechanical changes in tissue structures over a lifetime, many issues remain unresolved [3-8]. Current research lacks a comprehensive analysis of the physical mechanisms that drive the age-dependent variations in the mechanical properties of ligaments and tendons. The literature is particularly deficient in detailed studies that investigate the mechanistic

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relationships between structural changes and mechanical behavior over time. This gap in knowledge underscores the need for more rigorous and targeted research to elucidate the fundamental processes underlying these changes, which could significantly advance both clinical and material science applications.

Previous studies have shown that both the structure and the elastic modulus of tissues change with aging [6, 7, 9-13]. However, the relationship between tissue growth and mechanical properties is still unclear. Some researchers believe that cross-links between collagen fibrils in ligaments and tendons increase with age [8, 14], while others report that collagen cross-linking [15] and tissue stiffness decrease in older ages [9, 15, 16]. Experimental evidence suggests that the cross-sectional area of collagen fibrils increases with age and is directly related to the stiffness of the tissues [11, 12, 17].

To clarify these relationships, this research investigates the changes in mechanical properties and structural integrity of collagenous tissues, specifically ligaments and tendons, as they age using a modeling approach. The work develops innovative constitutive models that account for both mechanical and structural shifts during growth and maturation. The study identifies two distinct phases in the lifetime of these tissues: the growth phase, characterized by a rapid increase in the cross-sectional area of fibrils and the elastic modulus of fibers, and the mature phase, where these parameters stabilize.

The proposed models effectively illustrate the relationship between the increase in the cross-sectional area of fibrils, structural changes, and the elastic modulus of fibers over time. These models accurately characterize age-dependent tissues, covering both growth and mature phases. The parameters in the models have been validated with experimental data published by Goh KL et al. in 2018 [17]. The model calculations have shown good agreement with the results from these experiments.

This research provides a significant advancement in understanding the physical mechanisms governing the mechanical properties of ligaments and tendons by focusing on the role of collagen within fibrils. Through the development of novel mathematical models, we have established a direct correlation between collagen growth within fibrils and the increase in the elastic modulus of ligament and tendon fibers over time. These models reveal that the increase in the fraction of the cross-sectional area occupied by collagen within fibrils, as well as the overall expansion of the fiber's cross-sectional area, is linearly related to the enhancement of the elastic modulus. This new insight offers a deeper characterization of the structural-mechanical relationship within ligaments and tendons, providing a foundational framework for future research into tissue mechanics and the development of biomaterials.

Building on this foundation, the next section details the development of two key models: the collagen growth model, which tracks changes in the fraction of collagen within fibrils and the fiber's cross-sectional area, and the elastic modulus model, which describes the evolution of the fibers' elastic modulus over time. These models explicitly illustrate the relationship between collagen growth and mechanical properties. In the results and discussion section, model parameters are estimated through curve fitting with experimental data from [17], and their variations are analyzed to understand their roles. The relationship between collagen growth and elastic modulus is validated through this analysis. In the conclusions, we summarize our contributions and suggest directions for future research, emphasizing further model refinement and broader applications.

MATERIALS AND METHODS

Model formulation

In this study, the growth of ligaments and tendons is characterized by the function $\rho(t)$, which describes the increase of collagen in the tissues over time. This function represents the cross-sectional area of collagen in the fibrils assembled within a collagen fiber and the total cross-sectional area of the collagen fiber. A schematic of collagen growth within a collagen fiber is shown in Figure 1, where r denotes the radius of the collagen cross-sectional area increasing over time, while r_t and L represent the radius of the total cross-sectional area and the length of the fiber, respectively.

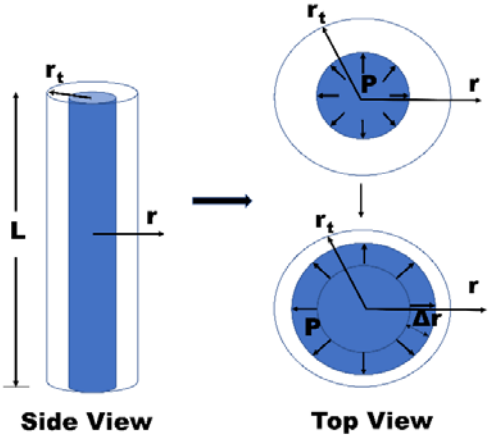

Figure 1 Structural illustration of collagen growth within a collagen fiber.

According to experimental data from a published study [17], $\rho(t)$ and the elastic modulus of the tissues, $E(t)$, increase rapidly during early ages and stabilize at the beginning of the mature ages. At this stage, $\rho(t)$ and $E(t)$ are denoted as ρ_m and E_m, respectively, and are considered constant. Therefore, in this study, ρ_m and E_m are treated as constants, while the variations of $\rho(t)$ and $E(t)$ are assumed to depend solely on the age of the tissues, t (measured in months). The detailed

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model formulation for $\rho(t)$ and $E(t)$ is described in the following section.

The growth model ($\rho(t)$)

We model the increase in collagen in the fibers over time using a rate equation. Therefore, the rate of change of $\rho(t)$ can be expressed as:

$$\frac{d\rho}{dt} = \frac{\rho_m - \rho}{\tau} \quad (1)$$

where τ is the constant relaxation time of tissues.

By rearranging equation (1) and integrating both sides, we can derive the expression for the growth function as follows:

$$\int_{\rho_0}^{\rho} \frac{d\rho}{\rho_m - \rho} = \int_{t_0}^{t} \frac{dt}{\tau} \quad (2)$$

$$\rho(t) = \rho_m - (\rho_m - \rho_0)e^{-\frac{(t-t_0)}{\tau}} \quad (3)$$

where ρ_0 and t_0 are the initial values of the collagen growth and the age of the tissues, respectively.

The elastic modulus model ($E(t)$)

Referring to the constitutive law of elastic materials in equation (4), where σ and ε represent the stress and strain in the collagen within the tissues, respectively, we can formulate a mathematical model for the elastic modulus of a collagen fiber in ligaments and tendons over time as follows:

$$\sigma = E(t)\varepsilon \quad (4)$$

Based on previous studies [17, 18], collagen in a collagen fiber is generated over time. To maintain a constant collagen density within the fiber, the increase in the cross-sectional area is attributed to the exerted force P distributed along the circumference of the collagen surface, causing an increase in the radius Δr in the r-direction, as shown in Figure 1. Consequently, the stress and strain due to this increase in the cross-sectional area of the collagen can be expressed as $\sigma = P/2\pi rL$ and as $\varepsilon = \Delta r/r$, respectively. Substituting these into equation (4), we obtain:

$$\frac{P}{2\pi rL} = E(t)\frac{\Delta r}{r} \quad (5)$$

Assuming that, for small deformations, the tissues behave as a linear elastic material obeying Hooke's Law (equation (4)), we can state that:

$$P = kr \quad (6)$$

where k is the stiffness constant of the collagen within the fiber.

By substituting equation (6) into equation (5) and rearranging, we obtain:

$$E(t) = \frac{kr}{2\pi rL} \times \frac{r}{\Delta r} \quad (7)$$

To express equation (7) as a function of $\rho(t)$, we multiply r/r to the right-hand side of equation (7) as follow:

$$E(t) = \frac{k}{2\pi L} \times \frac{r.r}{r.\Delta r} \quad (8)$$

For small deformations, we can approximate that $r.\Delta r \approx \int_0^{r_t} r dr = \frac{r_t^2}{2}$. Substituting this into equation (8), we obtain:

$$E(t) = \alpha\left(\frac{r^2}{r_t^2}\right) \quad (9)$$

where $\alpha = k/\pi L$ is a constant parameter of the model.

Recalling that $\rho = \frac{A}{A_t} = \frac{r^2}{r_t^2}$ and substituting it into equation (9), we obtain:

$$E(t) = \alpha\rho(t) \quad (10)$$

By substituting $\rho(t)$ from equation (3) into equation (10), we can finally derive the elastic modulus model of the tissues as:

$$E(t) = E_m - (E_m - E_0)e^{-\frac{(t-t_0)}{\tau}} \quad (11)$$

where $E_m = \alpha\rho_m$ and $E_0 = \alpha\rho_0$.

The relationship between elastic modulus (E) *and collagen fraction* (ρ) *in fibrils and the total fiber cross-sectional area*

The relationship between E and ρ can be expressed as follows:

By referencing the elastic modulus model presented in equation (11) and the growth model in equation (3), we derive Equations (12) and (13), respectively.

$$E(t) - E_m = -(E_m - E_0)e^{-\frac{(t-t_0)}{\tau}} \quad (12)$$

$$\rho(t) - \rho_m = -(\rho_m - \rho_0)e^{-\frac{(t-t_0)}{\tau}} \quad (13)$$

By dividing equation (12) by equation (13), we derive the following expression.

$$\frac{E - E_m}{\rho - \rho_m} = \frac{E_m - E_0}{\rho_m - \rho_0} \quad (14)$$

$$\frac{(E - E_0) + (E_0 - E_m)}{(\rho - \rho_0) + (\rho_0 - \rho_m)} = \frac{E_m - E_0}{\rho_m - \rho_0} \quad (15)$$

$$(E - E_0) = \left(\frac{E_m - E_0}{\rho_m - \rho_0}\right)[(\rho - \rho_0) + (\rho_0 - \rho_m)] - (E_0 - E_m) \quad (16)$$

By dividing equation (16) by $\rho - \rho_0$, the following expression is obtained.

$$\frac{E - E_0}{\rho - \rho_0} = \left(\frac{E_m - E_0}{\rho_m - \rho_0}\right)\left[1 + \frac{\rho_0 - \rho_m}{\rho - \rho_0}\right] - \left(\frac{E_0 - E_m}{\rho - \rho_0}\right) \quad (17)$$

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Thus, the relationship between E and ρ can be represented by the formula for the slope of the E - ρ curve, as follows:

$$\frac{dE}{d\rho} = \frac{\Delta E}{\Delta \rho} = \frac{E-E_0}{\rho-\rho_0} = \left(\frac{E_m-E_0}{\rho_m-\rho_0}\right) \quad (18)$$

Given that E_m, E_0, ρ_m and ρ_0 are constants, the slope of the E - ρ curve remains constant. This indicates a linear relationship between E and ρ.

By assuming the initial conditions, $E_0 = 0$ and $\rho_0 = 0$, we derive the following equation, which is consistent with Equation (10).

$$\frac{E}{\rho} = \left(\frac{E_m}{\rho_m}\right) = \alpha \quad (19)$$

Based on the model formulation presented above, the overall structure of the model system is illustrated in Figure 2.

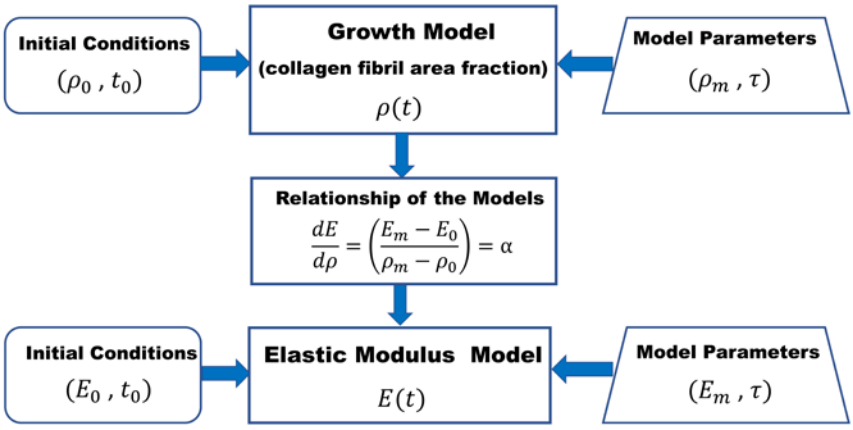

Figure 2 Schematic representation of the overall model system.

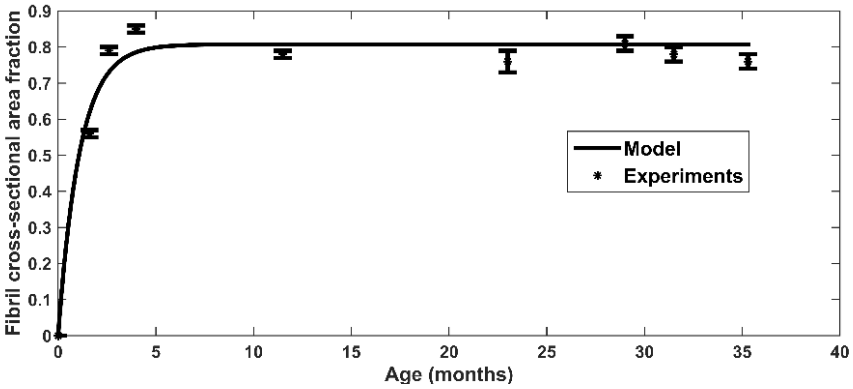

Figure 3 Experimental data showing the fraction of the cross-sectional area of collagen in fibrils and the total cross-sectional area of a fiber versus the ages of mouse tail tendons [17], along with the model fitting parameters $\rho_m = 0.8075$ and $\tau = 1.106$ months ($R^2 \approx 0.9744$).

RESULTS AND DISCUSSION

Parameter estimation of the growth model ($\rho(t)$)

To describe the growth and maturation behaviors of ligaments and tendons, the parameters (ρ_m, τ) in Equation (3) of the growth model need to be estimated. This study employed curve fitting between the mathematical model and experimental data from [17] to determine the appropriate values for these parameters.

The initial conditions for the model were set to $\rho_0 = 0$ and $t_0 = 0$. The model was then fitted to the experimental data, which included the fraction of the cross-sectional area of collagen in fibrils and the total cross-sectional area of a fiber plotted against the ages (in months) of mouse tail tendons, as reported in [17]. The curve fitting was performed using the Levenberg-Marquardt nonlinear least squares algorithm, implemented in Matlab (The MathWorks, Inc.). The parameter estimation results were found to be $\rho_m = 0.8075$ and $\tau = 1.106$ months, with a coefficient of determination $R^2 \approx 0.9744$.

As shown in Figure 3, the model fits well with the experimental data, accurately describing the characteristics of the growth and maturation behaviors of the tissues. According to the growth model (equation (3)), as $t \to \infty$, ρ approaches $\rho_m = 0.8075$, indicating that collagen growth eventually stabilizes at mature ages and becomes constant.

Parameter estimation of the elastic modulus model ($E(t)$)

The elastic modulus model (Equation 11) includes two parameters, E_m and τ. Given that τ was previously estimated as 1.106, we only need to estimate E_m to

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describe the stiffness behavior of ligaments and tendons over time. Therefore, we performed curve fitting between the mathematical model and the experimental results from the published study [17] to determine the appropriate value for E_m.

Assuming the initial conditions of $E_0 = 0$ and $t_0 = 0$, the model was fitted to the experimental data, which measured the elastic modulus of fibers against the ages (in months) of mouse tail tendons, as reported in [17]. Using the Levenberg-Marquardt nonlinear least squares algorithm in Matlab (The MathWorks, Inc.), we estimated E_m to be 580.8 MPa, with a coefficient of determination $R^2 \approx 0.9161$.

As illustrated in Figure 4, the model fits the experimental data well, accurately capturing the mechanical behavior of the tissues during both growth and mature ages. According to the elastic modulus model (Equation 11), as $t \to \infty$, E approaches $E_m = 580.8$ MPa, indicating that the elastic modulus of a collagen fiber stabilizes at mature ages.

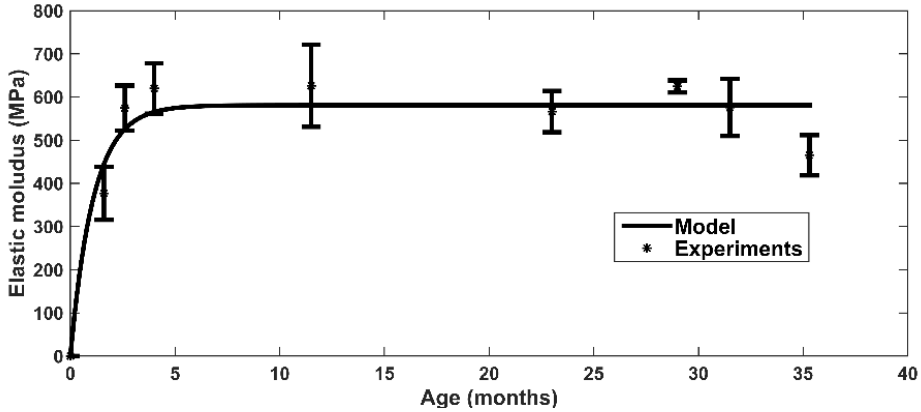

Figure 4 Experimental data showing the elastic modulus of a fiber versus the ages of mouse tail tendons [17], along with the model fitting parameters $E_m = 580.8$ MPa and $\tau = 1.106$ months ($R^2 \approx 0.9161$).

The curve fitting of the proposed models to the experimental data yielded $R^2 \approx 0.9744$ ($\pm 2.6\%$) for collagen growth and $R^2 \approx 0.9161$ ($\pm 8.4\%$) for elastic modulus, as shown in Figures 3 and 4, respectively. In biomechanics research, it is common to encounter significant data scatter, which can be influenced by factors such as the subject's age, tendon conditions, and specimen preparation processes [19]. For instance, a recent study [20] reported up to $\pm 30\%$ scatter in the values of the elastic modulus of human ligaments with aging. Similarly, another study [6] showed a polynomial function fitting to the experimental data of human tendon elastic modulus across all ages, with an R^2 of only 0.47 ($\pm 53\%$).

Given this context, the observed scatter in our model and experimental data, particularly the last data points in Figures 3 and 4 that deviate from the model calculations, falls within the expected range of experimental errors. However, further experimental data is necessary to validate these models fully. Additional data will also enable the extension of the models, potentially aiding in the development of age-appropriate interventions and treatments in fields such as orthopedics, rehabilitation, and sports medicine.

Estimation of the parameter relating the growth model to the elastic modulus model

According to Equation (10), the parameter α, which relates the growth of collagen in fibrils (growth model) to the variation in the elastic modulus of a fiber (elastic modulus model) over time, is a constant. From Equation (11), $E_m = \alpha \rho_m$, and using the previously estimated values of $\rho_m = 0.8075$ and $E_m = 580.8$ MPa, we can determine that $\alpha = 719.3$ MPa. This constant parameter α links the structural growth to the mechanical properties of collagen fibers, providing a unified framework for understanding the age-dependent behavior of ligaments and tendons.

Variation of the parameter, α, influencing the elastic modulus model

The variation of the constant parameter α, which represents the stiffness of the collagen in fibrils, influences the elastic modulus of fibers in ligaments and tendons. This relationship is illustrated in Figure 5.

As shown, when α increases, the elastic modulus in the mature region (E_m) also increases, while the time for the elastic modulus to stabilize (τ) remains unchanged.

Due to the linear relationship described by Equations (10) and (11), the behavior of α is consistent with the variations of the parameters E_m and ρ_m, which influence the elastic modulus and growth models, respectively. This implies that the primary factor affecting the elastic modulus of ligaments and tendons is the stiffness of the collagen in the fibrils.

As animals age, the amount of collagen in the fibrils increases. To maintain the same density of collagen, the cross-sectional area of the collagen fibrils must also increase. Therefore, the preserved density of collagen in the fibrils is a key property of the internal structure of ligaments and tendons, significantly influencing their elastic modulus.

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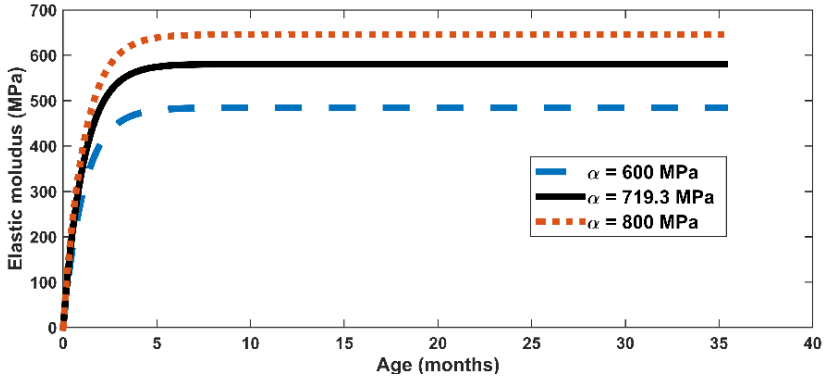

Figure 5 Impact of varying parameter α on the elastic modulus values of a fiber.

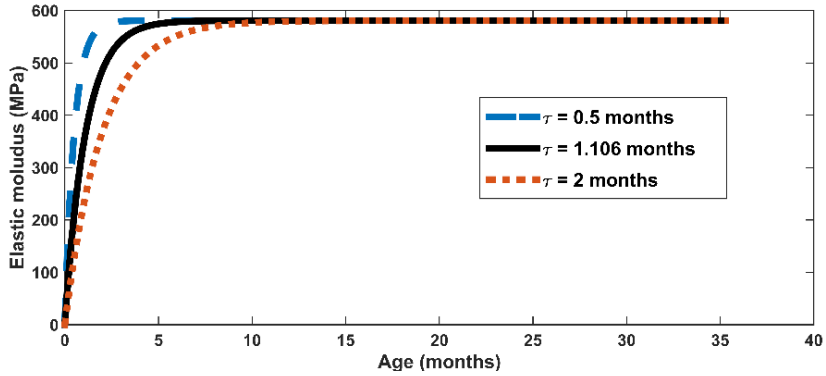

Figure 6 Impact of varying parameter τ on the elastic modulus values of a fiber.

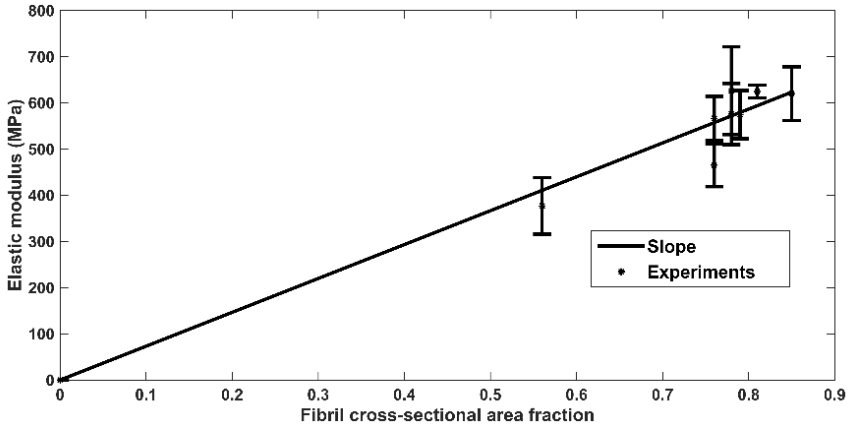

Figure 7 Experimental data depicting the relationship between elastic modulus and the collagen fraction in fibrils and the total fiber cross-sectional area [17], with the fitted slope parameter $\left(\frac{E_m - E_0}{\rho_m - \rho_0}\right) = 733.1$ MPa ($R^2 \approx 0.9554$).

Variation of the parameter, τ, influencing the elastic modulus model

The variation of the constant parameter τ, which represents the time required for the elastic modulus of fiber or the cross-sectional area of the collagen in fibrils to stabilize, impacts the elastic modulus values of fibers in ligaments and tendons. This relationship is illustrated in Figure 6.

As depicted, when τ increases, the age at which the elastic modulus stabilizes also increases, while the stable elastic modulus in the mature region (E_m) remains unchanged.

Since τ is the same in both Equations (3) and (11), the behavior of this parameter is consistent across both the growth and elastic modulus models. This indicates that the primary factor influencing the time it takes for E or ρ to stabilize in the mature region is the amount of collagen in the fibrils. As animals age, the collagen content in fibrils increases. To maintain a constant collagen density, the cross-sectional area of the collagen in the fibrils must also increase. Consequently, if the collagen growth is higher, it will take longer for the cross-sectional area of the collagen or the elastic modulus to stabilize. Therefore, the amount of growth collagen is likely a key factor in determining the relaxation time or the age at which tissues become mature.

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Estimation of the parameter governing the relationship between elastic modulus (E) and collagen fraction (ρ) in fibrils and the total fiber cross-sectional area

Based on Equation (18), the analysis reveals a linear relationship between E and ρ. The proportionality constant between these two parameters can be determined by the slope of the linear regression curve of E versus ρ, as demonstrated in Figure 7.

As illustrated in Figure 7, a linear relationship between E and ρ was established. The slope of the linear function was determined through curve fitting to the experimental data, incorporating the initial conditions, $E_0 = 0$ and $\rho_0 = 0$. The resulting slope was 733.1 MPa, which is in close agreement with the previously determined constant parameter $\alpha = 719.3$ MPa, indicating consistency with equation (19). This congruence between the two methods for estimating the constant parameter α offers valuable insights for the design of age-dependent experimental models in future research.

In Figures 3, 4, and 7, we present the experimental data with error bars representing the standard error of the mean (SEM). The values for the parameters ρ and E at each age were derived from the average measurements of 3-4 mouse specimens. As evidenced by the figures, the curves generated through our curve-fitting procedure closely align with the experimental data, consistently falling within the range of the error bars. This alignment underscores the robustness and reliability of the proposed models in accurately capturing the observed mechanical behavior. However, it is important to note that the goodness of fit, as reflected by the R^2 values, may improve with an increased sample size. A larger number of specimens would likely reduce variability and refine the precision of the parameter estimates, potentially yielding even stronger correlations between the models and the experimental data.

CONCLUSIONS

The experimental data [17] indicate that aging significantly affects the material composition and mechanical behavior of ligaments and tendons. Specifically, in these tissues, the fraction of the cross-sectional area of collagen fibrils and the total cross-sectional area of a collagen fiber-referred to as collagen growth-along with the elastic modulus of collagen fibers, increase rapidly during early ages (growth ages) and stabilize during middle and old ages (mature ages).

In this study, we presented mathematical models to describe these age-related changes in collagen growth and the elastic modulus of collagen fibers in ligaments and tendons. The parameters for these models were estimated using published data on mouse tail tendons [17]. Our model formulation, which assumes a constant stiffness of collagen, demonstrates that collagen growth (structural changes) is linearly related to the elastic modulus (mechanical property changes) of collagen fibers over time. Both models exhibit trends consistent with experimental data, including distinct growth and mature regions, as shown in Figures 3 and 4. The proposed elastic modulus model effectively captures the age-related trends of collagen fiber elasticity and explains the underlying mechanism of collagen growth influencing these mechanical changes.

Thus, our models provide a clear understanding of the growth mechanisms related to the mechanical properties of tissues as they age. This knowledge is crucial for comprehending the physiological origins of age-related changes in tissue components. A deeper understanding of these mechanisms can aid in addressing aging and developing preventive measures. Furthermore, the proposed models have potential applications in various aspects of age-dependent research.

Our findings indicate a linear, time-independent relationship between E (elastic modulus) and ρ (collagen fraction), highlighting the critical role of collagen quantity in tissue mechanics. This relationship, observed in mouse tail tendons, suggests that collagen's influence on mechanical behavior remains consistent over time. Future research should focus on extending this analysis to other species and tissue types to confirm the generalizability of this finding and provide a more comprehensive understanding of tissue mechanics across biological systems. Expanding experimental data in this way will enhance our ability to develop more robust, species-specific models with broader clinical and biomaterial applications. Additionally, future work will focus on extending these models to capture the declining elastic modulus in the aging phase and describe the mechanical characteristics of ligaments and tendons across different ages, reflecting the dynamic evolution observed in experimental data. This will enhance our understanding of the fundamental changes in connective tissues with age, paving the way for improved therapeutic interventions.

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