THE INLFLUENCE OF CROSS-LINKING ON THE DEFORMATION MECHANISM OF COLLAGEN FIBRILS

Julia Kamml(1), Chun-Yu Ke (2), Claire Acevedo(3, 4), David Kammer(1)

1. Institute for Building Materials, ETH Zürich, Switzerland; 2. Department of Engineering Science and Mechanics, Pennsylvania State University, USA; 3. Department of Mechanical Engineering, University of Utah, US; 4. Department of Biomedical Engineering, University of Utah, USA.

Introduction

Collagen type I is the main building component of various tissues. Its mechanical properties are directly derived from its structure of cross-linked tropocollagen (TC) molecules forming collagen fibrils. The cross-links are considered to be a key component of collagen fibrils as they can change the fibrillar behavior in various ways. While enzymatic cross-links (ECLs) are known for stabilizing the structure and improving the mechanical properties of the fibril and tissue, the accumulation of so-called Advanced-Glycation-Endproducts (AGEs) is associated with impaired material properties on the macroscale e.g. increased brittleness in bone. AGEs content in tissue has been observed to increase with aging and diabetes, some of the major concerns of western health systems, due to high glycation levels in the system. However, the mechanisms causing the deterioration in tissue behaviour remain unknown and the exact relationship between cross-link properties and fibrilar behavior is not well understood. Computational modelling can give insight into the nano-level structure of collageneous tissues, overcoming the limitations of imaging techniques in in-vitro studies, and providing a powerful tool for revealing the mechanical behavior of fibrils.

Methods

We use coarse-grained steered molecular models in order to evaluate the effect of AGE and ECL content on the mechanical behavior of the collagen fibril. Both types of cross-links are considered because AGEs mostly occur in aged or diabetic tissue where enzymatic cross-links are naturally present, since they have mostly been formed during growth and adult development. We build a 3D model of a representative part of the collagen fibril with 5 gap and overlap zones and a diameter of 20 nm, where the mechanical responses of TC molecules and cross-links are derived from reactive molecular dynamics simulations with atomistic resolution [1, 2]. We investigate the influence of cross-link density between TC molecules on stiffness, strength, and toughness (represented by work to failure) of collagen fibrils with a particular focus on AGEs increase on top of normal enzymatic cross-links.

Results

Our simulations show that the collagen fibrils stiffen at high strain levels beyond a certain strain limit when the AGEs content exceeds a critical value, while fibrils with lower AGEs density show softening mechanisms. In addition, the strength of the fibril increases with AGEs accumulation. We note that ECLs alone cannot cause the stiffened regime, but at low contents of AGEs cross-links may cause a stiffening of the collagen fibril that would not occur without them [2].
We analyze the force distribution within the TC molecules and the different types of cross-links (AGEs and ECLs) as well as their failure and demonstrate that a change of deformation mechanism is the origin of the stiffening and strengthening. A high AGEs content reinforces force transfer through AGEs cross-links rather than through friction between sliding tropocollagen molecules, which leads to failure by fracture of the tropocollagen molecules and sudden stress drops, causing a more abrupt failure of the collagen fibril [2].

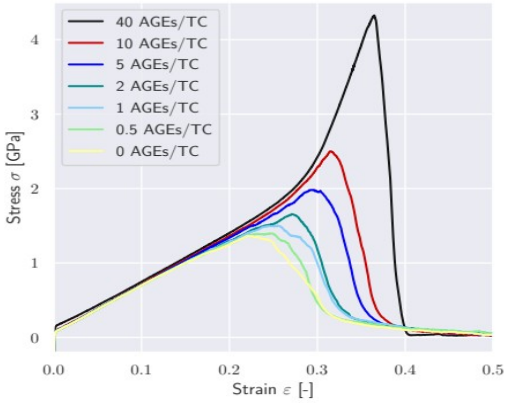

Figure 1: Stress-strain curves of tensile tests until rupture of a representative collagen fibril with different AGEs cross-link densities (0 ECLs) [2].

Discussion

Our results provide a direct and causal link between increased AGEs content, inhibited intra-fibrillar sliding, increased stiffness, and abrupt fibril fracture. Still, it would be important to provide experimental confirmation to better calibrate models and address limitations.

References

1. Depalle et al, J Mech Behav Biomed Mater, 52:1-13, 2015.
2. Kamml et al, Arxiv, arXiv:2301.13010v1, 2023