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The different distribution of enzymatic collagen cross-links found in adult and children bone result in different mechanical behavior of collagen

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ABSTRACT

Enzymatic collagen cross-linking has been shown to play an important role in the macroscopic elastic and plastic deformation of bone across ages. However, its direct contribution to collagen fibril deformation is unknown. The aim of this study is to determine how covalent intermolecular connections from enzymatic collagen cross-links contribute to collagen fibril elastic and plastic deformation of adults and children's bone matrix. We used *ex vivo* data previously obtained from biochemical analysis of children and adults bone samples ($n = 14$; $n = 8$, respectively) to create 22 sample-specific computational models of cross-linked collagen fibrils. By simulating a tensile test for each fibril, we computed the modulus of elasticity (E), ultimate tensile and yield stress (σ_u and σ_y), and elastic, plastic and total work (W_e, W_p and W_{tot}) for each collagen fibril. We present a novel difference between children and adult bone in the deformation of the collagen phase and suggest a link between collagen fibril scale and macroscale for elastic behavior in children bone under the influence of immature enzymatic cross-links. We show a parametric linear correlation between W_e and immature enzymatic collagen cross-links at the collagen fibril scale in the children population that is similar to the one we found at the macroscale in our previous study. Finally, we suggest the key role of covalent intermolecular connections to stiffness parameters (*e.g.* elastic modulus and W_e) in children's collagen fibril and to toughness parameters in adult's collagen fibril, respectively.

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1. Introduction

During childhood and adolescence, bone structure is altered by geometrical growth associated with increases in mass, and alterations in tissue density [13,61,62]. These processes build a bone with an optimal size, shape, and architecture to withstand the normal physiological loads that might come from children and teenagers' – subadults'— "tendencies to explore, fall over, off and out of things" [15]. Indeed, it has been established that their bone mechanical properties are different to adults' [9–11,13–15,17–18,42] and that might come from both genetic and environmental factors [59,60]. Furthermore, because the mechanical demand on children's bones is higher than in adults, it could be suggested that it is important for them to have a higher macroscopic toughness and stress-dissipation capacity of bones, rather than macroscopic stiffness [15,34].

Both immature (*i.e.* children) and mature (*i.e.* adults) bone tissues are composed mainly of an organic matrix of collagen (*i.e.* tropocollagen molecule — TC) with minerals (*i.e.* carbonated apatite nanoplatelets — cAp) and water. In connective tissues, such as bone and skin, TCs assemble into collagen fibrils and are stabilized by several posttranslational modifications that allow the formation of intermolecular and interfibrillar collagen cross-links (Fig. 1a–b) [6,7,21,70]. The two main kind of collagen cross-links depicted are enzymatic and non-enzymatic. Enzymatic collagen cross-links form intermolecular covalent liaisons between specific amino acids of tropocollagen helices to stabilize collagen fibrils [21,27,48,55,59,60]. They come from a physiological enzymatic pathway where the initial immature form links two collagen molecules together (*i.e.* hydroxylysino-norleucine (HLNL) and dihydroxylysino-norleucine (DHLNL)) (Fig. 1c). With time, immature enzymatic collagen cross-links further react with another collagen molecule to mature into a trivalent form (*i.e.* pyridinoline (PYD) and deoxypyridinoline (DPD)) (Fig. 1c). This conversion can be quantified as enzymatic collagen cross-links maturity which is defined by the ratio of trivalent (*i.e.* mature) and divalent (*i.e.* immature) cross-links

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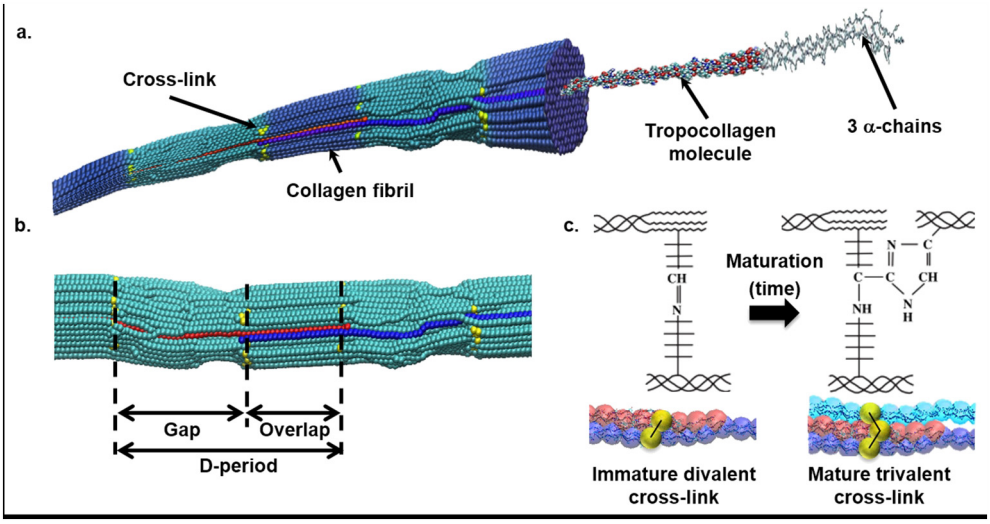

Fig. 1. (a) Hierarchical structure of a collagen fibril. (b) Representative section of the molecular model of ca collagen fibril. The characteristic gap and overlap region are clearly visible. (c) Representative forms of both divalent and trivalent cross-links (top) and representation in the molecular model (bottom). Over time, immature divalent cross-links will evolve into the mature trivalent form.

[11,48,57,65]. Enzymatic collagen cross-links can only form in few very specific locations of the terminal domains of the collagen molecule yielding a finite number of possible enzymatic collagen cross-links formation [63] and their density correspond to the amount of intermolecular covalent liaisons per mol. of collagen formed during this process. The chemical reactions leading to the formation of mature enzymatic collagen cross-links is a non-reversible continuous process [21,22,41,59,60,70], and effectively turns the individual tropocollagen molecules into a large interconnected polymer structure. Non-enzymatic collagen cross-links come from Glycation process and are depicted as Advanced Glycation End-products (AGEs). They are associated with aging or pathological conditions (diabetes) and impair collagen matrix normal function [3,31,74]. They can form in multiple locations along the length of the collagen and their density can be significantly larger that physiological enzymatic collagen cross-links [31,55]. Their positioning occurs randomly compared to enzymatic collagen cross-links [66,70], they accumulate with time where tissue turnover is slow [1]. Due to children's high bone turnover, AGEs are present in very few quantities in children's bone [11].

On one hand, TCs are mainly stabilized by intermolecular covalent liaisons from enzymatic collagen cross-links [6–7] to build a soft interconnected matrix [59,60,67]. On the other hand, the mineral phase is made of several cAp that nucleate inside the collagen matrix and link with TC [5,26,28] by several intermolecular forces [20], such as hydrogen or ionic bonds, to reinforce the soft matrix. Although enzymatic collagen cross-links, TC-cAp interface and water molecules have been shown to be determinants of the mechanical properties of bone; results are dependent on species, age, and testing method, making it difficult to understand their specific contributions. Indeed, experimental results on children's bone mechanical properties are very diverse [9,11,16,18,44,50] and there is still a gap of knowledge about the contribution of each bone element to children's bone mechanical behavior. In children population, pathologies affecting collagen such as lathyrism (an alteration of enzymatic collagen cross-links that does not affect the mineral [52]), Menkes disease (a deficient activity of lysyl-oxidase that causes defective in enzymatic collagen cross-linking [37]) and osteogenesis imperfecta (an alteration of collagen structure and enzymatic collagen cross-links that seem to be regulated independently to mineral crystallinity [65]), impact bone biomechanics and leads to pathological fractures. Therefore, understanding bone enzymatic collagen cross-links in children's bone is pivotal to improve both current therapies and diagnosis in children population affected by enzymatic collagen cross-links related bone pathologies.

Although previous results indicate that enzymatic collagen cross-links density in children bone is higher than in adult bone while enzymatic collagen cross-links maturity is lower [11,59,60], the respective contribution of enzymatic collagen cross-links density and maturity to bone deformation remains unclear in the children population. Our previous *ex vivo* mechanical tests of human bone samples have shown that enzymatic collagen cross-links maturity negatively correlates plastic energy dissipated before bone fracture at the macroscopic level. Our hypothesis is that *in silico* mechanical tests of collagen fibril – built from the data of the human bone samples previously tested — will show that enzymatic collagen cross-links maturity correlates with plastic energy dissipated before collagen fibril fracture. Furthermore, we anticipate that the evolution of both enzymatic collagen cross-links density and maturity is a significant contributor to collagen fibril mechanical behavior. To test our hypothesis, we have built 22 computational models from a mesoscale coarse-grained model of collagen fibrils [19] created using sample-specific enzymatic collagen cross-links data ((HLNL + DHLNL) and (PYD + DPD)) taken from biochemical analysis of bone samples of children and adults donors [11]. Collagen fibril mechanical properties (Modulus of Elasticity (E), ultimate and yield stress (σ_u, σ_y), strain for ultimate and yield stress (ε_u, ε_y) point elastic, plastic and total work (W_e, W_p and W_{tot})) have been obtained from computational tensile test to establish the link between collagen fibril elastic and plastic deformation and collagen fibril composition.

2. Materials and methods

2.1. Biochemical characterization

A total of 22 parallelepiped cortical bone samples (children samples n = 14 and adult samples n = 8) were obtained from fibula bones taken from 10 donors (7 children, ages = 11.6 ± 4.7 years and 3 adults, ages = 74.3 ± 9.9 years). The samples were then prepared to perform biochemical analysis to quantify the amounts of immature (HLNL + DHLNL) and mature (PYD + DPD) collagen cross-links. Details of experimental characterization can be found in our previous study [11].

2.2. Molecular model

A geometrically accurate mesoscale molecular model of a collagen fibril has been used in this study, in which a bead-spring model of a single tropocollagen helix has been replicated to form the collagen fibril (MATLAB r2014a, Mathworks Inc., Natick, MA, USA) [19] (Fig. 1). Both

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