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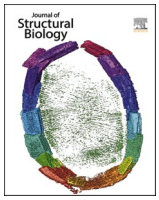

Mini review

On the role of the glycosylation of type I collagen in bone

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ABSTRACT

Glycan-protein interactions play a crucial role in biology, providing additional functions capable of inducing biochemical and cellular responses. In the extracellular matrix of bone, this type of interactions is ubiquitous. During the synthesis of the collagen molecule, glycans are post-translationally added to specific lysine residues through an enzymatically catalysed hydroxylation and subsequent glycosylation. During and after fibril assembly, proteoglycans are essential for maintaining tissue structure, porosity, and integrity. Glycosaminoglycans (GAGs), the carbohydrate chains attached to interstitial proteoglycans, are known to be involved in mineralization. They can attract and retain water, which is critical for the mechanical properties of bone. In addition, like other long-lived proteins, collagen is susceptible to glycation. Prolonged exposure of the amine group to glucose eventually leads to the formation of advanced glycation end-products (AGEs). Changes in the degree of glycosylation and glycation have been identified in bone pathologies such as osteogenesis imperfecta and diabetes and appear to be associated with a reduction in bone quality. However, how these changes affect mineralization is not well understood.

Based on the literature review, we hypothesize that the covalently attached carbohydrates may have a water-attracting function similar to that of GAGs, but at different lengths and timescales in the bone formation process. Glycosylation potentially increases the hydration around the collagen triple helix, leading to increased mineralization (hypermineralization) after water has been replaced by mineral. Meanwhile, glycation leads to the formation of crosslinking AGEs, which are associated with a decrease in hydration levels, reducing the mechanical properties of bone.

1. Introduction

Bone is a dynamic tissue that forms part our skeleton and provides structural support and protection of organs. Both the highly hierarchical structure and the composition of bones are vital to its ability to perform these functions. The extracellular matrix (ECM) is primarily composed of collagen type I that becomes mineralized with carbonated hydroxyapatite, but also contains non-collagenous proteins (NCPs), water, and a small amount of other collagen types (Fratzl, 2004).

The collagen molecule is a right-handed triple helix consisting of three left-handed polypeptide chains (two α1 and one α2 chains) of approximately 300 nm long. On the C-terminus as well as the N-terminal end, small non-helical domains are present – the telopeptides – that are needed for the collagen processing during biosynthesis and matrix assembly (Bächinger et al., 1993). The individual polypeptide chains are synthesized in the endoplasmic reticulum and have a repetitive motif of Gly-X-Y. The X and Y positions can be occupied by any amino acid but are most frequently proline and hydroxyproline, respectively (Gjaltema and Bank, 2017).

Many studies have been devoted to the investigation of the role of non-collagenous proteins (NCPs) in the bone biomineralization process (Boskey, 1989; Gorski, 2011). Even though these NCPs only make up a small percentage of the ECM (collagen type I comprises more than 90 % of the organic matrix), these proteins have an essential role in regulating the biomineralization and bone toughness (Glimcher, 1959).

A less explored part of the extracellular matrix are the carbohydrates, which are either mono- or disaccharides covalently attached to the collagen molecule, or the long glycosaminoglycan (GAG) chains of

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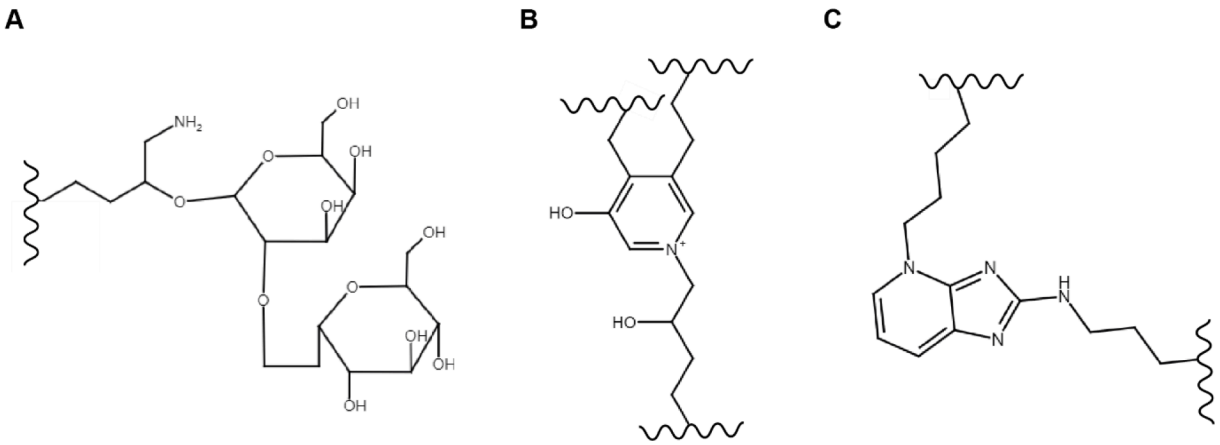

Fig. 1. Molecular structure of common post-translational modification. A) Enzymatic glycosylation of hydroxylysine resulting in glucosyl galactosyl hydroxylysine (GG-Hyl). B) The mature enzymatic pyridinoline crosslink. C) Non-enzymatic crosslink pentosidine as a result of glycation and subsequent formation of AGEs.

proteoglycans that non-covalently interact with the collagen. The combination of a protein core with one or multiple GAGs (e.g., chondroitin sulphate or dermatan sulphate in the case of decorin and biglycan, the two most abundant proteoglycans present in bone) result in the capability of proteoglycans to perform a variety of functions. The role of proteoglycans in bone formation have been extensively studied (Hao, 2022), and recently the presence of GAGs has been associated to the rate of collagen mineralization in dental tissue (Wojtas et al., 2020).

Here we review the role of collagen-attached carbohydrates both during matrix formation and its subsequent mineralization. We primarily focus on the possible roles of covalently attached carbohydrates in biomineralization arising from both enzymatic and non-enzymatic glycosylation but will also consider similarities in function of the indirectly bound GAGs of proteoglycans.

2. Post-Translational modifications of collagen type I in bone

The folding of the three collagen polypeptide chains into the triple helical conformation is rate limited by the peptidyl-prolyl cis–trans isomerisation, which is catalysed by the enzyme Cyclophilin B (Pyott, 2011). While the triple helix is being folded, multiple enzymes are responsible for its post-translational modifications (PTMs). The most prominent are the hydroxylation of proline (Pro) and lysine (Lys) and the subsequent glycosylation of the hydroxylysine-sites. The group of enzymes prolyl-3-hydroxylases (P3H) and prolyl-4-hydroxylases (P4H) convert Pro residues both in the X and Y position in the [Gly-X-Y] repeat to 3-hydroxyproline (3-Hyp) and 4-hydroxyproline (4-Hyp), respectively (Myllyharju, 2003). Where the function of the hydroxylation of Pro on the Y position into 4-Hyp is essential for the stability of the triple helix, the function of 3-hydroxylation of Pro on the X position is not well understood. Lysyl hydroxylase (LH) modifies both lysines on the Y position in the triple helix as well as lysines in the telopeptides that do not have the Gly-X-Y motif (Passoja, 1998). Hyl can subsequently be enzymatically glycosylated with a galactose to form galactosyl hydroxylysine (G-Hyl) (Sricholpech, 2011) and further with a glucose moiety to create glucosyl galactosyl hydroxylysine (GG-Hyl) (Fig. 1**a**) (Schegg, 2009). Osteoblasts from Cyclophilin B knock-out mice showed an increased GG-Hyl due to the delayed collagen folding that allowed prolonged enzymatic glycosylation, although no change in the hydroxylation of lysine residues was observed (Cabral, 2014). Although the sequence of events in collagen glycosylation has been elucidated, the precise function of this process remains elusive. Studies have suggested that glycosylation possibly stabilizes the collagen by mediating the interaction of the collagen with water (Bann et al., 2000).

After the secretion of the triple helical collagen molecules (tropocollagen) by the osteoblast into the extracellular space, they assemble in a quarter staggered fashion to create fibrils with a 67 nm repeat banding pattern showing a gap (±39 nm) and overlap (±28 nm) zone. During this process, specific Lys residues in the telopeptides are enzymatically converted to their aldehyde variant, allysine, under the influence the enzyme lysyl oxidase (LOX) (Cronlund et al., 1985; Knott and Bailey, 1998). Allysine can react with a Lys or Hyl on the triple helical domain to create bivalent crosslinks. These so-called immature crosslinks evolve spontaneously to the mature trivalent pyridinium or pyrrolic crosslinks (Fig. 1**b**), which are important determinants for the final bone quality (Saito and Marumo, 2010). Among pyridinium crosslinks, pyridinoline was one of the first maturation products identified. Pyridinoline has two forms: hydroxylysyl-pyridinoline (HP) formed from three Hyl residues and lysyl-pyridinoline (LP), derived from one Lys and two Hyl residues. Interestingly, the maturation of the immature crosslinks to either HP or LP is determined by its microenvironment (Terajima, 2014). The presence of carbohydrates at specific Hyl residues influences this microenvironment and inhibits the maturation of crosslinks, possibly by sterically hinderance of the bulky sugar groups (Yamauchi et al., 1986).

It was shown that where immature crosslinks have the same abundance of single and double glycosylation, mature crosslinks predominantly have the single glycosylation. It was suggested that this could be a result of the bulkiness of the double glycosylation which hinders or delays the condensation reaction (Terajima, 2014). Nevertheless, suppressing the LH3 enzyme in mice osteoblast led to a significant decrease in the abundancy of GG-Hyl, and concomitantly in a decrease of the amount of crosslinks. The observed increase in fibril diameter implies that through GG-Hyl glycosylation, the immature crosslinks play a role in the determining fibril diameter (Terajima, 2014).

Glycation, or non-enzymatic glycosylation, of collagen is a non-regulated reaction of a reduced glucose with the primary amine of lysine (Lys) or arginine (Arg). This age-related process results in the formation of advanced glycation end-products (AGEs) (Thomas, 2018; Gaar et al., 2020), of which some lead to the formation of crosslinks (Avery and Bailey, 2005). One example is pentosidine (PEN) (Fig. 1**c**) which forms crosslinks between two collagen molecules, and which due to its fluorescent properties is often used as a biomarker for AGE content. Besides crosslinking, glycation of collagen can lead to side-chain modification (e.g., carboxymethyl lysine), changing the charge of the Lys and Arg residues. This can subsequently lead to deformation in the collagen protein backbone by misalignment of the glycated residues (Goldberga et al., 2018).

Both enzymatic and non-enzymatic crosslinks play and important role in determining the mechanical properties of the collagen matrix, and hence of the resulting bone (Knott and Bailey, 1998; Saito and Marumo, 2015).

3. Glycosylation and bone quality

As discussed above, PTMs of the collagen matrix are strictly regulated and the amount, type and location of PTMs are very tissue specific. For example, there are large differences in the amount and GG-Hyl/G-Hyl ratio between the type I collagen of skin and bone. This suggests that these PTMs may play an important role in regulating matrix mineralization. Indeed, altered glycosylation is observed in different bone diseases (e.g., Osteogeneses Imperfecta (OI) (Taga, 2013; Raghunath et al., 1994), Ehlers Danlos type VI (Rohrbach, 2011; Steinmann et al., 2002) and related to increased fracture risk. Nevertheless, surprisingly little research has been conducted into the possible function of glycosylation in bone biomineralization.

An *in vitro* culture of osteoblasts from LH3 deficient mice with reduced GG-Hyl modifications (see previous section) showed a delay in the onset of mineral deposition, as detected with Alizarin Red (Sricholpech, 2012). As the loss of GG-Hyl modifications was especially prominent at the sides where mineralization is initiated, the authors hypothesized that this delay could possibly be due to altered interactions of the collagen with NCPs responsible for nucleation, or to the loss of GG-Hyl moieties that could be involved in regulating mineralization by interacting with other molecules that bind to the gap zones (integrins, proteoglycans, etc).

Glycation of collagen is prominent in patients with diabetes mellitus, where hyperglycaemia accelerates the formation of AGEs (King et al., 1998). Both diabetes type 1 (T1D – genetic) and type 2 (T2D – acquired) are associated with a higher bone fracture risk. However, where in T1D a reduction in bone mineral density (BMD) is observed, the BMD is not decreased in T2D implicating different mechanisms leading to bone fragility (Hygum et al., 2019). An *in vivo* study on diabetic rats showed that collagen fibrils display changes in their structure with increasing amount of AGEs, specifically affecting the gap regions (Odetti, 2000). The authors used atomic force microscopy (AFM) to analyse the collagen banding and observed an increase in depth of the gap zone cleft. The same results were observed for collagen samples that were exposed *in vitro* to high concentrations (0.5 M) of glucose. Also a TEM/AFM investigation on the molecular structure of collagen fibrils incubated in ribose-5-phosphate solution showed alteration in the molecular arrangements and fibril surface charge (Bansode, 2020). As the intermolecular channels of collagen were demonstrated to direct the crystal orientation during mineralization (Xu, 2020), glycation-induced changes in the collagen structure may possibly be related to bone fragility in diabetic patients. However, a 24-fold increase in glycation achieved by *in vitro* ribosylation of cortical bone showed no significant difference in the fracture toughness (Snow, 2023). Similarly, where *in vitro* ribosylation caused a 100 % increase in AGEs no effects on the fracture toughness of the bone were observed, even though Raman spectroscopy indicated changes of the secondary (helical) structure of bone collagen (Unal, 2023).

4. Glycosylation and hydration

In our bones, matrix-associated water can be identified at different hierarchical levels, where it has important functions in the regulation of formation processes as well as in regulating the mechanical properties of the resulting material (Wilson, 2006; Granke et al., 2015). At the microstructural level water is found in the bone pore network, whereas at the nanoscale water we find it loosely bound between multiple collagen fibrils. At the molecular level, tightly bound water forms hydrogen bonds between collagen peptide chains (Bella, 1994). Zooming in further, we find water trapped in the mineral phase, commonly is referred to as structural water (Wilson, 2006). While collagen-bound water is the most important contributor to the ductility of bone, also structural and pore water are essential for its mechanical properties (Bae, 2012). For example, water facilitates stiffness through increased porosity, extrinsic toughening mechanisms (e.g. crack deflection or ligament bridging) and the sliding of minerals over each other creating viscoelastic properties (Granke et al., 2015). Moreover, the compressive pre-stresses found in bone could be a result of the tensile stresses introduced by the replacement of water molecules with mineral during the mineralization of collagen (Bertinetti, 2015).

Carbohydrates display a great capability to attract and retain water in connective tissues and also in bone they play a crucial role in regulating the hydration of the matrix at the different hierarchical levels. Proteoglycans interact with collagen at the level of the fibrils where their GAGs regulate the hydration, which again is a strong determinant for tissue-level toughness (Wang, 2018). When the amount of proteoglycans decreases due to aging (17 %), the amount of bound water decreases significantly (40 %) (Wang, 2018).

At the molecular level it was shown that each triple helix contains a highly structured hydration shell which mediates the hydrogen bonding between the collagen molecules (Bella, 1994). One hierarchical level higher the interaction of the collagen with surrounding water molecules plays an important role in mediating the interactions between tropocollagen molecules during their assembly into fibrils (Giubertoni, 2024). To elucidate the role of glycosylation at the molecular level, molecular dynamic simulations of segments of collagen were carried out (Tang, 2020). These simulations showed that the hydrophobic faces of the carbohydrate moieties interact with either the hydrophobic side groups of the different amino acid residues or the hydrophobic backbone of the collagen, while their hydrophilic surfaces are facing towards the solvent. This controls both the protein backbone structure and the local structure of water molecules (Tang, 2020).

As carbohydrates are instrumental in attracting and retaining water molecules, an increase in the glycosylation could potentially also increase the hydration of the collagen molecules (Tang, 2020). Although it is not known whether there is a direct relationship between the level of collagen hydration and the degree of mineralization, it is known that mineralization involves the replacement of hydration water in and around the collagen fibrils (Olszta, 2007). As changes in the hydration level increases the amount of bound water, this may well result in different degrees of mineralization (Dorvee and Veis, 2013). It is interesting to speculate if and how the increased levels of glycosylation observed in OI bones relate to the reported hyper-mineralization (Roschger, 2008).

In contrast, the accumulation of AGEs in aging cortical bone due to increased glycation is inversely related to the amount of bound water (Nyman, 2008). *In vitro* experiments indicated that the decrease in the amount of bound water as a result of increasing AGEs concentrations results in weaker bones (Nyman, 2019). However, we must note that the activation of the signal pathway by the AGE receptor (RAGE) in combination with high glucose levels has been shown to influence osteoblast activity, so that there may be multiple pathways responsible for the observed loss of bone quality (Asadipooya and Uy, 2019).

5. Conclusion and future directions

Glycosylation and glycation are two different mechanisms for the modification of collagen with carbohydrates. Where glycosylation occurs intracellularly before collagen assembly, glycation occurs over time in the extracellular space. Although both pathways have been associated with bone fragility, little is known about the underlying mechanisms.

One important common function associated with carbohydrates in bone is the regulation of the level of hydration at the different hierarchical levels of the bone matrix. Hydration of collagen molecules, fibrils and tissues plays an important role in bone biomineralization as well as in determining mechanical properties. Where this is well established for the role of proteoglycans (Bertassoni and Swain, 2014), the role of glycosylation and glycation are less well understood.

From the reviewed literature and the comparison with the role of GAGs in proteoglycans we can hypothesise the following effects of collagen glycosylation and glycation on bone structure and quality.

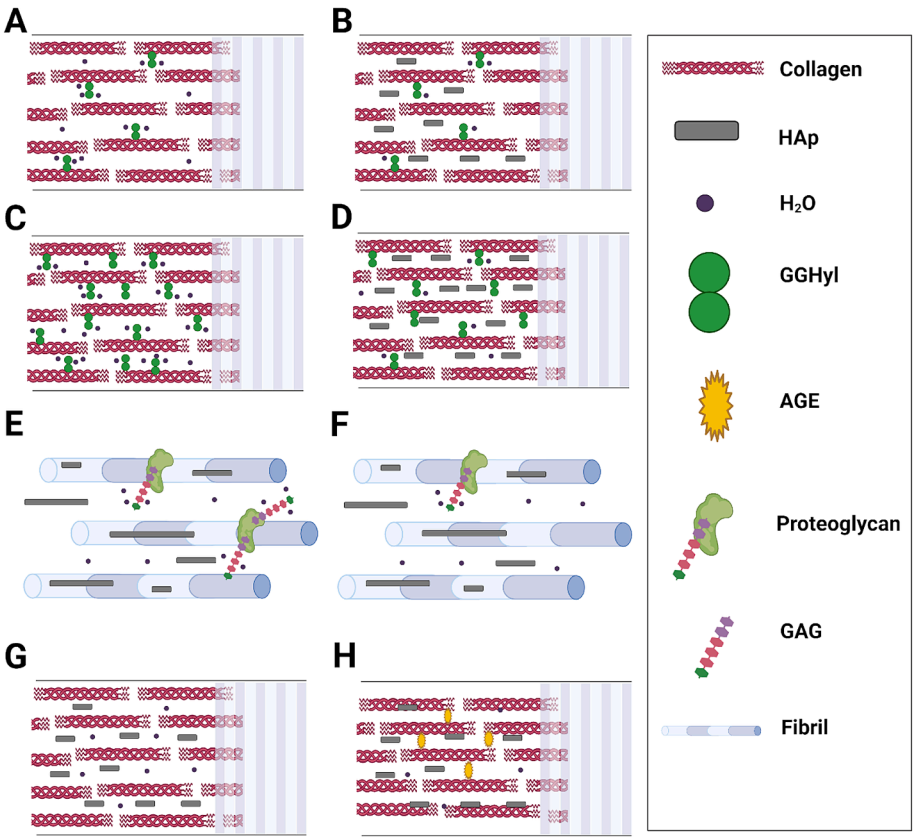

Fig. 2. Schematic representation of the possible mechanism by which carbohydrates influence hydration and subsequent bone strength. A) Collagen assembled in its quarter staggered arrangement. B) Mineralization of the collagen by the substitution of water molecule by carbonated hydroxyapatite (cHAp) mineral. C) Over-glycosylation of collagen possibly resulting in the extra hydration of the collagen molecules. D) Extra water molecules and space in the fibril are replaced by mineral resulting in hypermineralization. E) Normal mineralized bone where proteoglycans are located between the collagen fibrils and attract water. F) Loss of proteoglycans (as a result of aging) weakening the bone by the loss of bound water. G) Normal mineralized collagen fibrils in bone. H) Glycation of bone resulting in the formation of AGE crosslinks leading to dehydration of the bone.

Glycosylation provides the collagen molecules with increased hydrophilicity and thereby regulates the solvation of the triple helix. As collagen mineralization involves the replacement of water with calcium phosphate mineral, the degree of hydration of collagen will be essential for this process (Fig. 2**a-b**). Over-glycosylation, as for example reported for OI bone could potentially lead to a higher degree of hydration, hence leaving room for over-mineralization of the matrix (Fig. 2**c-d**).

The loss of proteoglycans and the concomitant to the loss off interfibrillar water leads to a reduction of bone mechanical properties during aging of the individual (Fig. 2**e-f**) (Wang, 2018). Additionally, aging leads to increased glycation of bone collagen resulting in the formation of AGEs, a process that can be accelerated by diseases such as diabetes. Also the increasing amount of AGEs is associated with dehydration of the bone (Willett et al., 2022), as well as with a reduced bone strength (Poundarik, 2015). Besides, non-mineralized collagen is dehydrating with increasing amount of crosslinks (Kopp et al., 1990) and chemical crosslinking of collagen leads to a loss of water by the tighter packing of the collagen fibrils (Miles, 2005). Possible reasons for the loss of the mechanical properties of bone due to AGE formation could be a reduction of molecular space imposed by the AGE crosslinks, that limit the hydration of the collagen (Fig. 2**g-h**).

To investigate these hypotheses, we will need to acquire a deeper understanding of the collagen interactions on the molecular and nanostructural scale (Bertassoni, 2012). The *in vitro* model systems, which are already developed to investigate the effect of glycation on the fibril structure (Bansode, 2020), could be extended to investigate the effect of glycation on collagen mineralization at the smallest length scales. In particular (solid-state) nuclear magnetic resonance ((ss)NMR) spectroscopy will be a powerful technique to elucidate the mechanisms by which collagen uses associated carbohydrates to interact with the water and mineral, since the technique can probe the collagen conformations, (non)-enzymatic modifications as well as the molecular structure of mineral and its collagen interface (Murgoci and Duer, 2021). Additionally, NMR can probe the mobile and bound water of a mineral matrix (Nyman, 2008), but also its proximity to glycosylation species on the collagen (Chow, 2014).

Complemented by high-resolution information that is nowadays available from cryo-electron microscopy, it has the potential to discover the role of carbohydrates on collagen type I biomineralization in health and disease. Addressing this issue will have significant impact on biomedical and therapeutic strategies towards several bone-related diseases.

CRediT authorship contribution statement

Luco Rutten: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Elena Macías-Sánchez:** Writing – review & editing, Supervision. **Nico Sommerdijk:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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