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Review

Measurement of aminoterminal propeptide of type I procollagen (PINP) in serum

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ABSTRACT

The aminoterminal propeptide of type I procollagen (PINP) in serum is a sensitive indicator of the synthesis of type I collagen. Four assays are available for PINP, two of them (intact PINP assays) measure the intact propeptide and the other two (total PINP assays) also detect a smaller antigen in serum. In many clinical situations, these assays give similar information, but renal insufficiency increases the concentration of the smaller antigen, influencing both the apparent concentration of PINP and assay calibration.

Serum PINP is mostly affected by changes in bone metabolism. In infants and children, the concentration is much higher than in adults. Serum PINP (s-PINP) is a useful indicator of disease activity in Paget's disease of bone, in bone metastases of osteoblastic nature, and in the follow-up of treatment of osteoporosis. The IFCC and IOF recently recommended the use of s-PINP as a reference marker for bone formation in studies concerning fracture risk assessment and treatment response.

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Introduction

Bone formation begins as osteogenesis during prenatal development and continues throughout life as part of the bone turnover cycle. Osteoblasts are the cells responsible for producing both the organic matrix of bone and several factors that regulate its mineralization. In cultured osteoblastic cells, three consecutive phases have been identified in the development of the phenotype: proliferation, extracellular matrix maturation, and matrix mineralization [1], type I collagen being the major protein product of the first phase. This collagen comprises more than 90% of the organic matrix of mineralized bone, and about 70% of all collagens in the body. In the extracellular matrix of soft tissues, type I collagen is usually found together with other collagens, particularly type III collagen, which, however, is absent from mineralized matrix.

Fibres of type I collagen consist of rod-like molecules that are regularly aligned in a parallel, quarter-staggered fashion and become covalently cross-linked to each other. Each molecule consists of two identical α1 chains and one slightly different α2 chain, wound around one another into a collagen-specific triple-helical conformation [2,3]. The biosynthesis of such molecules is a complex process as a number of posttranslational modification reactions are needed to render the protein with the characteristics necessary for its correct conformation and cross-link formation. The molecules have a capacity to spontaneously aggregate to fibrils and fibres. In order to keep the molecules in solution before adequate fibre formation, type I collagen is synthesized as a larger precursor, type I procollagen, that carries large propeptide domains at both ends. These are set free en bloc before fibril formation and form the basis for measuring the synthesis rate of type I collagen.

Origin of PINP — biosynthesis of type I collagen

The genes encoding the two polypeptide chains of type I procollagen are on different chromosomes, COL1A1 on chromosome 17 and COL1A2 on chromosome 7 [2,3]. The translation of the corresponding mRNAs takes place on membrane-bound ribosomes. The nascent polypeptide chains proceed into the lumen of the endoplasmic reticulum (ER), where they are modified in a series of enzymatic posttranslational modification reactions. The assembly of the chains to a trimeric molecule takes place in the cisternae of the ER, starting from the carboxyterminal propeptide domains of the chains, and is strengthened by disulfide bridges between these parts. The major triple helix of the molecule forms spontaneously, and the most aminoterminal domain, the aminoterminal propeptide, is the last to assume its native conformation. The formation of the helix stops the posttranslational modification reactions in the ER. The most important one of these reactions is the hydroxylation of prolyl residues to 4-hydroxyproline, as the latter is necessary for the stability of the triple helix at body temperature, both in the collagen proper and in the helical part of the aminoterminal propeptide.

The structure of a type I procollagen molecule is shown in Fig. 1. In the extracellular space, two specific enzymes release the propeptide domains from the protein. The removal of the bulky, globular carboxyterminal propeptide is a necessary prerequisite for the assembly of the collagen to fibrils, whereas the aminoterminal, more rod-like propeptide can for some time remain attached to part of the collagen molecules, which are on the surface of the fibrils. As the fibril grows in thickness, the removal of the aminoterminal propeptides also reaches completion.

The propeptides, generally abbreviated as PINP and PICP for amino- and carboxyterminal propeptide respectively, are two different proteins, yet produced in equimolar amounts with each other and with the collagen deposited in the tissue. E.g. in an acute fibroproliferative reaction, such as that taking place when type I collagen expression is induced in a healing wound, there is an identical, dramatic increase in the concentrations of both propeptides in the extracellular fluid of the wound space [4]. Despite being called propeptides, both are in fact quite sizeable proteins.

Type I collagen biosynthesis takes place particularly in fibroblasts and osteoblasts, in the former during fibroproliferative responses and in the latter as the first part of bone matrix production. In total, between 400 and 1200 g of collagen is produced in the body of an adult human per year, most of it being type I collagen. This indicates that between 150 and 500 g of propeptide material is set free in the same time, about one third of this being PINP and the rest PICP.

Another molecular species of type I collagen, so-called type I α1-trimer collagen, has been found in some pathological tissues, e.g. breast cancer [5], osteoarthritic bone [6], as well as lesions producing pleural or ascitic fluid. This molecule consists of three identical α1(I) chains, whereas the more common molecule is a heterotrimer of two types of chain (see below). Although a homotrimeric PINP can be isolated from pleural effusion [7], present PINP immunoassays do not distinguish between the heterotrimeric and homotrimeric isoforms of the propeptide.

Properties and metabolism of PINP

The aminoterminal propeptide of type I procollagen consists of three subunit chains that are non-covalently linked to each other — two pro-α1 chains and one pro-α2 chain [2,3]. The molecular mass of the whole protein is about 35,000, and those of its constituent chains 14,250 and 5500, respectively. The pro-α1 chain has three structurally different domains: an aminoterminal globular domain which resembles the C repeat of von Willebrand factor, a central domain of a short collagenous triple helix, and a very short carboxyterminal domain. The pro-α2 chain is shorter as it lacks the N-terminal globular domain. The most immunogenic part is the globular domain.

As type I collagen is being synthesized in osteoblasts and deposited as osteoid in the resorption cavity, the release of the aminoterminal propeptide may be somewhat delayed and takes place at the latest during the matrix maturation phase of osteoblast development. In bone the free propeptide probably has direct access to the blood. The rate of bone turnover is related to the number of active bone remodelling units in the skeleton, which shows wide inter-individual variation. This is in accordance with the fact that the reference intervals for biochemical bone turnover markers, including PINP, tend to be broad.

Although the biosynthetic events of type I collagen are similar in bone and soft tissues, the circulating concentrations of the corresponding procollagen propeptides seem to be mostly affected by the former. First, most of this collagen in the body is in the skeleton. Second, the turnover rate of skeletal collagen exceeds that of most soft

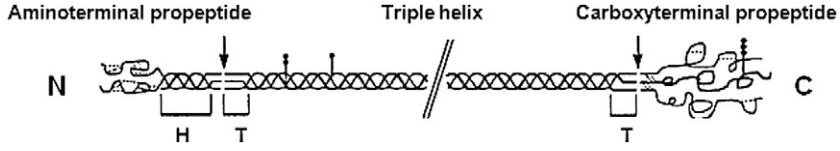

Fig. 1. Structure of the type I procollagen molecule. The arrows indicate the sites of proteolytic cleavage of the aminoterminal (PINP) and carboxyterminal (PICP) propeptides. H = helical domain of the aminoterminal propeptide and T = telopeptides at both ends of the collagen proper.