Editorial

Biomarkers of Joint Damage in Rheumatoid Arthritis: Where Are We in 2013?



The search for biomarkers identifying key targets for the assessment of major outcomes in chronic diseases has become one of the most interesting topics of research in different areas of clinical medicine, in particular in oncology, hematology, and rheumatology. In rheumatoid arthritis (RA), one of the leading causes of disability among chronic diseases, possible biomarkers should help the rheumatologist to identify (in very early or early RA) the patients who are going to respond quickly and favorably to disease-modifying antirheumatic drugs (DMARD), those not responding to DMARD and receiving biologic therapies (among which there is great need of biomarkers to choose a "personalized" biologic agent), those not responding to any of the several biologics, and finally, in all the previous settings, those who will develop structural damage more rapidly. Currently, researchers have great interest in the field of "personalized medicine," which should allow physicians to optimally match patient with treatment[1]. The ideal biomarker should be similar to glycated hemoglobin (i.e., target for HbA1c less than 7)[2], which gives significant information on the metabolic status of the patient with diabetes before and after therapy, particularly the metabolic status that allows or prevents progression of vascular damage in terms of diabetes-related comorbidities such as acute myocardial infarction, stroke, or diabetic nephropathy[3].

Pathology

RA is characterized by synovitis and joint tissue destruction, including cartilage loss and bone erosion, with variability in outcome in different patients, that is, a self-limiting disease in some, and one characterized by progressive joint destruction in others. Biomarkers could be devised to define the aggressiveness of synovitis and to monitor the structural damage, or there could be 1 ideal biomarker summarizing both aspects. The possibility of identifying the individual RA patient's future disease severity could guide the choice of the best treatment strategy and during the disease course could guide treatment modifications to stop joint damage, cartilage destruction, and bone resorption. At this level disease progression is generally monitored through plain radiographs, which provide an indirect, semiquantitative measure of cartilage loss and bone damage[4,5], while ultrasound and magnetic resonance imaging (MRI) are now under investigation. However, when the radiologic diagnosis is established, there often already is significant joint damage. With respect to cartilage, delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) and T2 mapping have shown potential to define the amount of glycosaminoglycan content of articular cartilage through 7 Tesla MRI[6].

Alternatively, molecular markers "describing" the synovial, cartilage and bone turnover, and metabolic activity could be useful to identify patients with RA who are at high risk of rapid disease progression. Several studies have been performed assessing the possible use of different markers as measures of synovial inflammation and bone damage in RA. Among them, degradation products of collagen such as the pyridinium crosslinks pyridinoline (PYD) and deoxypyridinoline (DPD) are 2 well-characterized biochemical markers of bone resorption. PYD and DPD are formed during bone maturation because of the formation of lysine-hydroxylysine crosslinks between different collagen molecules and during degradation of mature bone collagen. PYD and DPD are released into the circulation and cleared into the urine. They are some of the markers of bone resorption used to define overall bone turnover (Table 1), along with bone formation markers.

Other studies have assessed the PYD and DPD levels in RA patients; significantly higher total PYD concentrations have been found in the synovial tissue of patients with active RA compared to patients with inactive RA or osteoarthritis (OA), indicating an elevated crosslinking density of mature synovial tissue collagen with increased activity in RA. Moreover, the study of multiple biological compartments in these patients revealed that the urinary concentration of PYD was related to disease activity,

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The Journal of Rheumatology 2013; 40:8; doi:10.3899/jrheum.130566

Table 1. Markers of bone turnover.

Bone Resorption	Bone Formation† Bone Formation Inhibitors*
Hydroxyproline	† Total alkaline phosphatase
Collagen crosslinks	† Bone alkaline phosphatase
Pyridinolines (pyridinoline, deoxypyridinoline)	† Osteocalcin
Crosslinked telopeptides (NTx, CTx)	† Procollagen type I propeptides
Trap5b (tartrate resistant acid phosphatase)	† Osteoprotegerin
Cathepsin K	* DKK-1
RANKL	* Sclerostin

RANKL: receptor activator of nuclear factor kappa ligand; the main stimulator of mature osteoclasts; cathepsin K: the main osteoclastic protease; DKK-1: Dickkopf-1; inhibits differentiation of osteoblasts; sclerostin: antagonizes osteoblast differentiation by blocking the Wnt pathway.

showing a simultaneous increase with increasing synovitis[6]. Immunological and chromatographic methods have been developed to measure these compounds in the urine and serum with a 10:1 ratio[7]. Despite some analytical variability, the data show no significant differences in the precision of chromatographic versus immunological methods[7,8].

Pyridinoline as a biomarker

In this issue of *The Journal*, Krabben, *et al*[9] evaluate the predictive value of serum PYD levels for actual and future joint destruction in patients with RA, at baseline for longterm prediction and during the disease course for near-term prediction. The observed association between PYD serum levels and severity of joint damage was found to be independent of other risk factors (such as anticitrullinated protein antibodies or C-reactive protein levels) for the progression of joint damage. Direct correlation between baseline PYD serum levels and serum levels during the disease course could confirm that RA patients with more severe radiological progression had increased PYD serum levels at the beginning and throughout the disease. This finding suggests its possible future use in RA followup, similar to that of HbA1c in diabetes. Moreover, demonstration of the association between PYD serum levels and joint space narrowing and erosion rate confirms that association for both cartilage loss and bone damage, because PYD exists in both cartilage and bone.

In a conservatively treated, community-based cohort of patients with very early arthritis (31% with RA), Le Loët, *et al* found a strong association between serum levels of IgA-rheumatoid factor (IgA-RF) and serum PYD concentrations, measured with high-performance liquid chromatography (HPLC), and unequivocal erosion (grade ≥ 1) at 2 years[10]. These authors used a prediction model with IgA-RF thresholds of 5 and 25 IU/ml and a PYD threshold of 10 nM/l, reaching an OR value of 50.75 for the association of IgA-RF > 5 IU/ml and PYD > 10 nM/l able to predict > 1 erosion at 2 years. Thus, it seems that a definite value of 10 nM/l could be the warning level for the occurrence of future erosions.

Analyzing results obtained in the past with HPLC, data suggest that no real difference could be observed when testing patients with grade 1 or grade 4 Steinbrocker class[11], implying that the overall structural damage (cartilage plus bone) could not easily be extracted in practice.

However, the interpretation of PYD (and DPD) levels in urine is hampered by biologic and other preanalytical and analytical variabilities[12]. The effects of analytical variability can be minimized through standardization of results of laboratory measurements, by controlling imprecision through the use of good laboratory standard practices, and by validating proper method calibration. Still, the interlaboratory (much less intralaboratory) coefficients of variation are high and need to be refined. These strategies are currently being implemented for PYD (and DPD), as stated above, as well as for other bone markers[13]. Moreover, there are possible confounding factors in the interpretation of results obtained from PYD measurements, which could be influenced by other concomitant diseases and conditions.

Pyridinoline and confounders

The recommendations are to dose and interpret urinary PYD (and DPD) considering several factors along with bone diseases, such as menstrual cycle, physical activity, diet, seasonal variation, and geographic differences affecting PYD (and DPD) biologic variability[14]. Some pathological processes associated with RA, such as osteoporosis, infection of internal organs, cardiovascular (CV) disease, coexisting osteoarthritis, or concomitant corticosteroid treatment, may contribute to increased crosslink excretion[15,16]. DPD has been detected in CV muscle and aorta, confirming that its distribution is not restricted to bone and dentin, as previously thought. Heart failure has been associated with disturbances affecting bone metabolism and predisposing to exacerbated bone loss[17], and elevated levels of collagen-derived molecules belonging to the bone degradation pathway were detected in patients with CV diseases[18]. Most importantly, PYD can be increased with type I as well as type II and III collagen degradation.

In the study by Krabben, *et al*[9], patients with RA were not stratified according to the presence of comorbidities; but it might be important, in daily practice, to consider among other factors the CV comorbidities and osteoporosis and RA in the interpretation of PYD and DPD levels, because these collagen-derived markers seem to signal expression of more severe disease and a link to CV comorbidities.

Unmet need of PYD to consider before defining it a possible biomarker of damage

In clinical practice, the ideal biomarker (e.g., HbA1c) should be "objectively measured and evaluated as an

Table 2. Characteristics of the ideal biomarker and of PYD in rheumatoid arthritis.

Biomarker	Ideal (i.e., HbA1c)	PYD
Objectively measured	+	+
Indicator of normal biology	+	+
Indicator of the pathologic process	+	+
Indicator of response to therapy	+	?
Indicator of prognosis	+	+
Indicator of modification of the pathologic process	+	?
Sensitive and specific	+	–

PYD: pyridinium crosslinks pyridinoline.

indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" and thus should give the physician clear information on the status of the disease, the chances of modifying the outcome, and the prognosis. Therefore it should be sensitive and specific, give rapid results (HbA1c provides a 3-month average of percentage of blood that is glycated), be of clinical value in guiding therapy, and have prognostic significance. PYD thus has only some of the characteristics of the ideal biomarker (Table 2).

The assessment of cartilage and bone remodeling markers in RA remains a challenge; and we await the appearance of the ideal biomarker to use in clinical practice, one that will provide the prognostic information that enables us to take therapeutic decisions.

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J Rheumatol 2013;40:1244–6; doi:10.3899/jrheum.130566