Collagen Type II Cleavage Assay (C2C ELISA)

Cat. # 60-1001-001

Brief literature review of some publications where IBEX C2C ELISA assay was used.

- Sera from patients with rheumatoid arthritis (RA) reveal increases in C2C level over controls. Moreover, compared to RA patients with slow radiographic changes, those with rapid radiographic progression over a 4 year period had persistently elevated levels in sera of C2C, C12C and CS846 but not CPII. The values after one year predicted subsequent progression, especially in the case of C2C. (Verstappen *et al,* 2006).

- Another RA treatment study showed that the serum ratio of C2C : CPII was decreased in early RA on treatment with infliximab, compared to baseline, regardless of the EULAR response grade . The ΔC2C : CPII over 54 weeks correlated with the changes in CRP, DAS28 levels, radiographic progression and patient function (HAQ). But C2C : CPII remained unchanged in established RA. These results suggest that the ability to control cartilage type II degradation (C2C) and promote its synthesis is most effective in early RA. (Niki *et al,* 2012).

- Balance between serum type II collagen (C2C) and type I collagen (C1,2C) degradation products and synthesis of type II collagen (CPII) revealed that after 1 month of biologic treatment, changes in these three biomarkers predicted radiographic outcome in 88% of patients after 1 year. An increase in C2C alone at 1 month predicted radiographic progression at 1 year. Clinical remission was predicted by a decline in serum C2C at 1 month. (Mullan *et al,* 2007).

- Studies of serum C2C have revealed no detectable changes following the menopause in contrast to increases in the bone biomarkers bone alkaline phosphatase and cross-linked type I collagen N-telopeptide. (Kojima *et al,* 2008).

- Using MRI, positive correlations were observed between the C2C serum assay and cartilage degeneration in male OA knee T2 images (King *et al*, 2004). Increases in serum C2C and C1,2C, but not CPII and CS846, are associated with radiographic knee OA (Kong *et al,* 2006) reflecting the increased cleavage of type II collagen by collagenases viewed *in situ* in diseased joints. (Wu *et al*, 2002; Dejica *et al,* 2012).

- When knee or hip OA patients were haplotyped for mitochondrial haplogroups , the C2C, CPII and the C2C : CPII ratio were significantly increased in sera of OA patients carrying the haplogroup H compared to OA carriers of the J haplogroup (Fernandez-Moreno *et al,* 2012). The collagenase MMP-13 is also more elevated in patients of the more common haplogroup H who are more likely to need total joint replacement than non-H haplotypes (Soto-Hermida *et al,* 2015).

- In a study following knee ACL rupture, in which baseline serum pre-injury were available, subsequent serum changes in C2C, C12C, CPII and CS846 were observed compared to age-related changes in uninjured controls (Svoboda *et al,* 2013).

- Patients at increased risk for ACL rupture can be identified prior to injury by differences in serum C2C, C12C, CPII and CS846 levels (Svoboda *et al,* 2016). These findings suggest that fundamental genetic and/or biomechanically related differences exist that influence cartilage metabolism.

- Arthroscopic analyses of pre-radiographic knee cartilage degeneration following ACL injury have revealed significant associations of increased synovial fluid C2C with the presence of three or more high Outerbridge graded cartilage lesions (Yoshida *et al,* 2013).

Collagen Type II Cleavage Assay (C2C ELISA)

Cat. # 60-1001-001

1. Dejica VM, Mort JS, Laverty S, Percival MD, Antoniou J et al. (2008). Cleavage of type II collagen by cathepsin K in human osteoarthritis cartilage. Am J Pathol 173: 161-169.
2. Dejica V, Mort JS, Laverty S, Antoniou J, Zukor DJ et al. (2012). Increased type II collagen cleavage by cathepsin K and collagenase activities with aging and osteoarthritis in human articular cartilage. Arthritis Res Therapy 14: R113.
3. Fernandez-Moreno M, Soto-Hermida A, Oreiro N, Pertega S, Fenandez-Lopez C et al. (2012). Mitochondrial haplogroups define two phenotypes of osteoarthritis. Front Physiol 3:129
4. King KB, Lindsey CT, Dunn TC, Ries MD, Steinbach LS, Majumdar S. (2004). A study of the relationship between molecular biomarkers of joint degeneration and the magnetic resonance-measured characteristics of cartilage in 16 symptomatic knees. Magn. Reson. Imaging 22: 1117-1123.
5. Kojima T, Kojima M, Noda K, Ishiguro N, Poole AR. (2008). Influences of menopause, aging and gender on the cleavage of type II collagen in cartilage in relationship to bone turnover. Menopause 15: 133-137.
6. Kong SY, Stabler TV, Criscione LG, Elliott AL, Jordan KM, Kraus VB. (2006). Diurnal variation of serum and urine biomarkers in patients with radiographic knee osteoarthritis. Arthritis Rheum 54: 2496-2504.
7. Mullan RH, Matthews C, Bresnihan B, Fitzgerald O, King L et al. (2007). Early changes in serum type II collagen biomarkers predict radiographic progression at one year in inflammatory arthritis patients after biologic therapy. Arthritis Rheum 56: 2919-2928.
8. Niki Y, Takeuchi T, Nakayama M, Nagasawa H, Kurasawa T et al. (2012). Clinical significance of cartilage biomarkers for monitoring structural joint damage in rheumatoid arthritis patients treated with anti-TNF therapy. PLoS One 7: e37447
9. Soto-Hermida A, Fernandez-Moreno M, Pertaga-Diaz S, Oreiro N, Fernando-Lopez C et al. (2015) Mitochondrial DNA haplogroups modulate the radiographic progression of Spanish patients with osteoarthritis. Rheumatol. Int 35: 337-344.
10. Svoboda SJ, Harvey TM, Owens BD, Brechue WF, Tarwater PM, Cameron KL. (2013). Changes in serum biomarkers of cartilage turnover after anterior cruciate ligament injury. Am J Sports Med 41: 2108-2116.
11. Svoboda, SJ, Owens, BD, Harvey TM, Tarwater,PM, Brechue WF Cameron, KL. (2016). Biomarkers of collagen turnover and subsequent anterior cruciate ligament rupture. Am J Sports Med. 44: 1687-1693.
12. Verstappen SMM, Poole AR, Ionescu M, King LE, Abrahamowicz M et al. (2006). Radiographic joint damage in rheumatoid arthritis is associated with differences in cartilage turnover and can be predicted by serum biomarkers: an evaluation from 1 to 4 years after diagnosis. Arthritis Res Therapy 8: R31.
13. Yoshida H, Kojima T, Kurokouchi K, Hanamura H et al. (2013). Relationship between pre-radiographic cartilage damage following anterior cruciate ligament injury and biomarkers of cartilage turnover in clinical practice: a cross-sectional observational study. Osteoarthritis Cartilage 21:831-838.
14. Wu W, Billinghurst RC, Pidoux I, Antoniou J, Zukor D et al. (2002). Sites of collagenase cleavage and denaturation of type II collagen in aging and osteoarthritic articular cartilage and their relationship to the distribution of matrix metalloproteinase 1 and matrix metalloproteinase 13. Arthritis Rheum 46: 2087-2094.