CONCISE REPORT

Procollagen IIC-peptide as a marker for assessing mechanical risk factors of knee osteoarthritis: effect of obesity and varus alignment

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Abstract

Objective—To ascertain by cross sectional examination whether the concentration of procollagen IIC-peptide in joint fluid significantly correlates with mechanical risk factors of knee osteoarthritis (OA), such as obesity (body mass index) and varus alignment (lateral femorotibial angle).

Methods—The concentrations of procollagen IIC-propeptide in synovial fluid were measured by a sandwich enzyme immunoassay of 65 patients with the same radiological stage of primary knee OA—that is, Ahlbäck stage I. The relations between procollagen IIC-peptide and body mass index and lateral femorotibial angle were examined using simple regression analysis and multiple regression analysis.

Results—Significant positive correlations were found between procollagen IIC-propeptide concentrations and body mass index ($r=0.479$, $p<0.0001$), and between procollagen IIC-propeptide concentrations and lateral femorotibial angle ($r=0.375$, $p=0.0021$). Significant correlations were also found by multiple regression analysis. The multiple correlation coefficient of body mass index and femorotibial lateral angle to the procollagen IIC-propeptide concentrations was 0.547 ($p<0.0001$).

Conclusions—The findings suggest that synthesis of type II collagen by chondrocytes is enhanced by abnormal mechanical stress, in this case obesity and varus alignment. It is concluded that procollagen IIC-propeptide concentrations in joint fluid are a useful marker of early OA. (*Ann Rheum Dis* 2000;59:982-984)

collagen synthesis, it is expected to be useful in monitoring the condition of osteoarthritic cartilage.¹⁻³ We therefore conducted cross sectional examinations to ascertain whether the concentration of procollagen IIC-peptide in joint fluid is significantly correlated with mechanical risk factors of knee osteoarthritis (OA), such as obesity and varus alignment.

Methods

Sixty five patients with the same radiological stage of primary knee OA—that is, Ahlbäck stage I, were examined. All patients were diagnosed according to the clinical and radiographic criteria of idiopathic knee OA provided by the American Rheumatism Association.⁵ Their average age was 64 (SD 11) years. Only eight of the 65 patients were men.

Joint fluid samples were aseptically obtained from the patients' knee joints. The fluids were centrifuged at 10 000 rpm for 20 minutes to remove cell and tissue debris, and the supernatants were stored at -80°C . Procollagen IIC-peptide concentrations in the joint fluid were determined by a one step sandwich enzyme immunoassay as previously described.² The assay was linear between 0.2 and 20 ng/ml. Intra- and interassay variability was 4-5%.

The following variables were assessed: the relation between joint fluid procollagen IIC-propeptide concentrations and obesity/varus alignment. Obesity was assessed by the body mass index (BMI).⁶ This is the ratio of weight in kilograms to height in metres squared—the index of relative weight named by Keys, which he considered preferable to other indices of relative weight. Among Japanese people a BMI between 19.8 and 24.2 is normal, 24.2-26.4 is considered overweight, and more than 26.4 indicates obesity.⁷ Varus alignment was assessed by determination of the femorotibial lateral angle (FTA) by leg radiography carried out while the patient was standing on one leg. Tamaki and Koga conducted prospective field research among Japanese people⁸ and reported that in 203/820 cases no osteoarthritic change to the knee joints according to the x ray results had taken place either before or after seven years' follow up. The mean FTA was 173.9 (3.1) degrees and the mean (SD) age 55.4 (5.4) years.

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Assessment of the condition of articular cartilage in osteoarthritic knee joints is important for early diagnosis and evaluation of the effects of treatment. Although radiography and magnetic resonance imaging allow assessment of the degree of bone and cartilage attrition morphologically, joint fluid molecular markers serve as a method of metabolic assessment. As procollagen IIC-peptide is a marker of type II

Simple regression analyses were carried out to assess the correlation between procollagen IIC-propeptide concentrations and BMI, and between procollagen IIC-propeptide concentrations and FTA. Multiple regression analysis was also performed. In particular we sought to establish whether procollagen IIC-propeptide concentrations correlate with the linear addition of BMI and FTA ($a \times \text{BMI} + b \times \text{FTA}$). p Values <0.05 were considered significant.

Results

The mean BMI was 24.4 (4.0) (range 14.8–36.9). This mean lies within the range denoting overweight among Japanese people. The mean FTA was 178.5 (5.8) degrees (range 170–192). This mean was slightly larger than the mean FTA of Tamaki's normal group. Because the correlation between BMI and FTA was not

significant ($r=0.249$, $p=0.682$), biomechanical BMI and FTA are considered independent mechanical factors.

The mean concentration of procollagen IIC-propeptide in the joint fluid was 4.0 (3.2) ng/ml. This value was significantly higher than that previously determined by the same method using knee joint fluid from healthy volunteers.⁹

Significant positive correlations were found between procollagen IIC-propeptide concentrations and BMI ($r=0.479$, $p<0.0001$, fig 1), and between procollagen IIC-propeptide levels and FTA ($r=0.375$, $p=0.0021$, fig 2). Significant correlations were also found by multiple regression analysis (table 1). The multiple correlation coefficient of the procollagen IIC-propeptide concentrations to $(0.355 \times \text{BMI} + 0.153 \times \text{FTA} - 31.405)$ was 0.547 ($p<0.0001$).

Discussion

Procollagen IIC-propeptide is a non-collagenous carboxypeptide extension of type II procollagen molecules. During the formation of type II collagen fibrils, this extension is removed and released from type II procollagen molecules, implying that procollagen IIC-propeptide release into joint fluid reflects type II collagen synthesis by chondrocytes. This is supported by the findings of Nelson's report.¹⁰ He found that the synthesis of type II collagen in the cartilage correlated with the content of procollagen IIC-propeptide in both the cartilage and the culture medium in vitro using human and bovine cartilage. He also reported that the content of procollagen IIC-peptide in articular cartilage is highest in fetal cartilage, being reduced almost threefold at birth and reaching low levels in normal adult cartilage; but in human OA cartilage it was significantly raised.¹⁰ In osteoarthritic knee joints the concentrations of procollagen IIC-propeptide in the joint fluids were found to be higher than in the joint fluids of healthy volunteers.⁹ We therefore examined whether procollagen IIC-propeptide concentrations in primary knee OA are correlated with risk factors.

We limited this investigation to early stage knee OA only—namely, to Ahlbäck stage I knees. Because the articular cartilage is worn out in knees with advanced OA, the variability of the condition of the articular cartilage is likely to affect adversely an investigation of whether mechanical factors correlate with procollagen IIC-propeptide concentrations in joint fluid.

A variety of risk factors have been reported for primary OA, such as body weight,¹¹ sex,¹² working environment,¹³ and heredity.¹⁴ All these factors may influence type II collagen synthesis by chondrocytes. Felson, in his epidemiological analysis based on the Framingham study,¹¹ reported that obesity as a mechanical risk factor was closely related to the incidence of knee OA. This was supported by our formerly reported research using joint fluid procollagen IIC-propeptide concentrations.¹ We consider that varus alignment is another independent mechanical risk factor of OA because as the severity of the varus alignment

Figure 1 Correlation between procollagen IIC-peptide concentrations and body mass index (BMI). Procollagen IIC-propeptide concentrations in joint fluid were measured by enzyme immunoassay. Significant correlations were found between procollagen IIC-propeptide concentrations in joint fluid and BMI in 65 patients with primary knee osteoarthritis, Ahlbäck stage I ($r=0.479$, $p<0.0001$).

Figure 2 Correlation between procollagen IIC-peptide concentrations and lateral femorotibial angle (FTA). Significant correlations were also found between procollagen IIC-propeptide concentrations in joint fluid and the FTA in 65 patients with primary knee osteoarthritis, Ahlbäck stage I ($r=0.375$, $p=0.0021$).

Table 1 Results of multiple regression analysis among procollagen IIC-propeptide concentration, body mass index (BMI), and femorotibial lateral angle (FTA)

	Std Error	t Value	p Value
BMI	0.089	3.751	0.0004
FTA	0.062	2.483	0.0157
Constant	10.654	-2.948	0.0045

Procollagen IIC-propeptide concentration (ng/ml) = $0.355 \times \text{BMI} + 0.153 \times \text{FTA} - 31.405$.

of the knee joint increases the more the mechanical stress caused by body weight concentrates on the medial compartment of the knee joint, even if the body weight is the same.

Our findings suggest that synthesis of type II collagen by chondrocytes is enhanced by abnormal mechanical stress such as obesity and varus alignment as both were significantly positively correlated with procollagen IIC-propeptide concentrations. We conclude that procollagen IIC-propeptide concentrations in joint fluid are a useful marker of early OA and reflect mechanical risk factors.

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