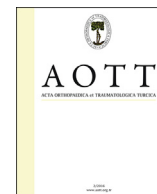




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## Serum and knee synovial fluid matrix metalloproteinase-13 and tumor necrosis factor-alpha levels in patients with late stage osteoarthritis

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### ABSTRACT

**Objective:** To compare the levels of MMP-13 and TNF- $\alpha$  in late stage osteoarthritis, define their predominant pathways and investigate their correlation with McMaster Universities Arthritis Index scores. **Patients and methods:** A total of 42 patients (mean age  $64 \pm 8.8$ ) with grade 3 and grade 4 knee osteoarthritis according to Kellegren- Lawrence criteria and who were scheduled for total knee arthroplasty were enrolled in the study. TNF-alpha and MMP-13 levels were measured preoperatively from venous blood samples and intraoperatively from knee synovial fluid via ELISA. Preoperative and 1 month postoperative knee functions were assessed by McMaster Universities Arthritis Index.

**Results:** Grade 4 synovial fluid MMP-13 ( $4.76 \pm 5.82$ ) was elevated compared to grade 3 ( $3.95 \pm 4.45$ ) ( $p = 0.438$ ), whereas grade 3 serum MMP-13 ( $1.128 \pm 0.308$ ) was found elevated compared to grade 4 ( $1.038 \pm 0.204$ ) ( $p = 0.430$ ). Grade 4 serum TNF- $\alpha$  ( $0.253 \pm 0.277$ ) was elevated compared to grade 3 ( $0.206 \pm 0.219$ ) whereas grade 3 synovial fluid TNF- $\alpha$  ( $0.129 \pm 0.052$ ) was elevated compared to grade 4 ( $0.118 \pm 0.014$ ). Positive correlation was observed between synovial fluid MMP-13 levels and post-operative WOMAC scores. Mean serum TNF- $\alpha$  level ( $0.226 \pm 0.246$  pg/ml) was found higher compared to synovial level ( $0.124 \pm 1.59$ ), synovial MMP-13 level ( $4.31 \pm 1.24$ ) was found higher compared to serum level ( $1.089 \pm 1.519$ ).

**Conclusion:** Despite the systemic increase in TNF- $\alpha$  levels concordant with osteoarthritis grade, MMP-13 levels are elevated via local manner with a significant correlation with WOMAC scores.

**Level of evidence:** Level IV, Diagnostic study.

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### Introduction

Although Osteoarthritis (OA) is generally known to be a common disease among the elderly, mainly involving the cartilage, recent data suggest an important role for subchondral bone and synovial membrane in its pathogenesis and initiation of the disease.<sup>1–3</sup> Furthermore, periarticular and bifocal localized dens bony islands are also proven to initiate cartilage erosion and contribute to OA progression.<sup>4</sup> The influence of instability and abnormal

tibiofemoral kinematics on joint cartilage loading can start complex pathophysiologic mechanisms that lead to cartilage degradation.<sup>5,6</sup> Extracellular matrix (ECM) turnover is regulated by matrix metalloproteinases (MMP) that degrade essential ECM proteins. MMP's are secreted from macrophage, fibroblast and chondrocytes via the stimulatory effect of Interleukin-1beta (IL-1 $\beta$ ) and Tumor Necrosis Factor-alpha (TNF- $\alpha$ ). Studies reveal significant elevated MMP 1,3,9,13 levels in the subchondral bone, cartilage and synovial membrane specimens in osteoarthritic patients compared to control groups and degradation of ECM has been proven to be initiated mainly by MMP's, secreted from chondrocytes.<sup>7,8</sup> Besides MMP's, pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , IFN-gama become active as, increase in mechanical stress on joint cartilage can initiate the inflammatory phase.<sup>9–12</sup> TNF- $\alpha$  is known to be the

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most potent and active cytokine secreted from M1 macrophages in response to IL-1 and bacterial toxins (e.g lipopolysaccharide).<sup>13–15</sup> In a study conducted by Alaaeddine et al, compared to non-arthritic tissues, elevated TNF- $\alpha$  receptors were found in chondrocytes and synoviocytes derived from osteoarthritic joints. Chondrocytes derived from osteoarthritic joints also upregulated TNF- $\alpha$  receptors in normal human chondrocytes when incubated together.<sup>16,17</sup> 100 microgram (99 m) Tc human anti-TNF antibody was used to bind TNF- $\alpha$  receptors and elevated levels of TNF- $\alpha$  was detected in arthritic joints using scintigraphy in OA and Romatoid Arthritis patients.<sup>18</sup>

Although various proinflammatory cytokines described above have been defined to play a major role in OA pathogenesis, up to date, comparison between local/systemic MMP-13, TNF- $\alpha$  levels in grade 3–4 osteoarthritic knees and their relation with WOMAC scores have not been investigated. In addition to environmental and patient specific factors, we believe that MMP-13, TNF- $\alpha$  are the 2 major mediators in OA progression. The aim of the study is to compare serum, synovial fluid levels of MMP-13, TNF- $\alpha$  in two different grades of the disease, identify their correlation with McMaster Universities Arthritis Index (WOMAC) and define their possible predominant pathways (local – systemic).

## Material and methods

42 patients (38 female, 4 male), mean age  $64 \pm 8.8$  years with grade 3 and grade 4 knee OA according to Kellgren–Lawrence criteria were enrolled in a prospective interventional clinical study with secondary data analysis. Patients with DM, Addison disease and under any medication that could effect the cytokine profile were excluded from the study. 10 patients were previously diagnosed with HT with blood pressures regulated with medical treatment. All patients were hospitalized 2 day prior surgery for preoperative planning, received s.c. low molecular weight heparin 12 h before surgery and the same diet. All patients had a history of sedentary life style due to pain, none experienced trauma and were related with any kind of sports activity and during their hospitalization were not allowed strenuous activity that could effect inflammatory cytokine levels prior surgery.

All patients underwent single stage bilateral posterior cruciate ligament retaining total knee replacement surgery. Preoperative 3 cc venous blood sample was taken from the antecubital vein from each patient just before the first tourniquet was inflated. The time of day the blood samples collected were synchronized and all patients underwent surgery as the first patient at 8:00 am with a maximum delay of 5 min. Synovial fluid samples were collected with a needle intraoperatively from each knee after the capsule was exposed. TNF- $\alpha$  and MMP-13 levels were analyzed using Enzyme Linked Immunosorbent Assay (ELISA). Immediately after collection, samples were centrifuged 10 min at 1500 rpm at the operating room and stored at  $-80^\circ$ . Collection, storage of the samples were carried out using the same protocol for each patient. Preoperative and 1 month postoperative knee functions were assessed by WOMAC score. WOMAC index is compromised of 24 parameters that include; pain (score range 0–20), stiffness (score range 0–8) and functional impairment (score range 0–68).<sup>19</sup>

Preoperative and postoperative WOMAC knee function scores from 42 patients were correlated with serum TNF- $\alpha$ , MMP-13 and synovial fluid TNF- $\alpha$ , MMP-13 levels. The significance between serum and synovial fluid MMP-13 levels, serum and synovial fluid TNF- $\alpha$  levels were evaluated separately both in grade 3 and 4 patients. Significance between serum TNF- $\alpha$ , synovial fluid TNF- $\alpha$  and serum MMP-13, synovial fluid MMP-13 levels was analyzed between grade 3 and grade 4 patients. Statistical comparisons were generated using Statistical package for Social Sciences-11 for

Windows programme (SPSS, Chicago,IL,USA). All data are expressed as means  $\pm$  SD. Paired sample T test was used to evaluate preoperative and postoperative follow-up data, whereas Student's t Test was used to analyze the significance of MMP-13 and TNF- $\alpha$  levels at the 2 different grades of OA. Pearson correlation coefficient was used to analyze the correlation between WOMAC scores and variables from TNF- $\alpha$  and MMP-13 levels. P values less than 0.05 were considered statistically significant.

The current study was approved by the local ethical committee and informed consent form was obtained from each patient.

## Results

In both grade 3 and 4, mean TNF- $\alpha$  levels ( $0,226 \pm 0,246$  pg/ml) were found to be significantly higher compared to mean synovial fluid TNF- $\alpha$  levels ( $0,124 \pm 1,59$ ) ( $p = 0,011$ ). Contrary to the above finding, mean synovial fluid MMP-13 levels ( $4,31 \pm 1,24$  pg/ml) were found to significantly higher compared to serum MMP-13 levels ( $1089 \pm 1519$ ) ( $p = 0,001$ ) (Table 1). Compared to serum, synovial MMP-13 levels were found to be high both in grade 3 and grade 4 whereas TNF- $\alpha$  was found to be higher in synovial fluid compared to serum in grade 3 but higher in serum compared to synovial fluid in grade 4 (Table 2). Compared to grade 3 ( $3,95 \pm 4,45$ ), grade 4 synovial fluid MMP-13 ( $4,76 \pm 5,82$ ) was elevated, whereas grade 3 serum MMP-13 ( $1128 \pm 0,308$ ) was found elevated compared to grade 4 ( $1038 \pm 0,204$ ) ( $p = 0,438$ ,  $p = 0,430$ ). Compared to grade 3 ( $0,206 \pm 0,219$ ) grade 4 serum TNF- $\alpha$  ( $0,253 \pm 0,277$ ) was elevated whereas, grade 3 synovial fluid TNF- $\alpha$  ( $0,129 \pm 0,052$ ) was elevated compared to grade 4 ( $0,118 \pm 0,014$ ). ( $p = 0,548$ ,  $p = 0,363$ ). There was no significant correlation between preoperative WOMAC ( $69.9 \pm 7.3$ ), postoperative WOMAC index ( $40.2 \pm 14.5$ ) and serum, synovial fluid TNF- $\alpha$  and serum MMP-13 levels and also between preoperative WOMAC Index and synovial fluid MMP-13. Contrary to blood MMP-13 levels, a positive correlation was observed between synovial fluid MMP-13 levels and postoperative WOMAC scores ( $p = 0,038$ ,  $r = 0,321$ ) (Table 3).

## Discussion

There is now strong evidence that the structural changes, globally observed in OA are due to a combination of mechanical factors and biochemical pathways. Despite the ongoing advanced molecular studies, the pathophysiology of OA and factors that contribute to disease progression is still unknown. Experimental studies reveal that there is an ongoing inflammatory process that triggers both anabolic and catabolic events.<sup>20</sup> Recently, several specific mediators such as; MMP-13, MMP-3, IL-1 $\beta$ , IFN-gama ve TNF- $\alpha$  have been distinguished from synovial membrane and joint cartilage to explain the pathophysiological mechanisms leading to OA and to elucidate their potential use in detecting the extent of the disease.<sup>21</sup> A model of human culture of synovial cells from digested osteoarthritis synovium demonstrated that both inflammatory and destructive response are cytokine-driven through a combination of IL-1 and TNF- $\alpha$ .<sup>22</sup>

Several variables including obesity, diurnal rhythm, diet, medications, collection-storage of samples, time point of collection,

**Table 1**

Mean serum and knee synovial fluid TNF- $\alpha$  and MMP-13 levels of osteoarthritic patients.

	Serum	Synovial fluid	p
TNF- $\alpha$ (n = 42)	$0,226 \pm 0,246$	$0,124 \pm 1,59$	0,011
MMP-13 (n = 42)	$1089 \pm 1519$	$4,31 \pm 1,24$	0,000

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