Background: Circumscribed cartilage defects are considered as prearthritic lesions and lead to differential intra-articular cytokine expression. Mechanisms of associated pain development and influence of smoking behavior are not yet fully understood in humans.

Purpose: This study aimed to reveal relations between synovial cytokine levels in knees with circumscribed cartilage defects and pain sensation.

Study Design: Descriptive laboratory study.

Methods: In a clinical trial, knee lavage fluids of 42 patients with circumscribed cartilage lesions treated by either microfracturing (n = 19) or by autologous chondrocyte implantation (n = 23) and fluids of 5 healthy control individuals were prospectively collected. Preoperative knee pain was evaluated according to frequency and strength; subjective knee function was assessed using a visual analog scale and the International Knee Documentation Committee (IKDC) score. Synovial concentrations of aggrecan, insulin-like growth factor (IGF)-I, basic fibroblast growth factor (bFGF), interleukin (IL)-1β, bone morphogenetic protein (BMP)-2, and BMP-7 were determined by enzyme-linked immunosorbent assay.

Results: Pain strength showed a highly significant association with intra-articular IGF-I levels (p = .48, P < .01), but no correlation with synovial concentrations of aggrecan, bFGF, IL-1β, BMP-2, and BMP-7. Although pain strength and frequency demonstrated a statistically significant relationship, no substantial association between pain frequency and any of the examined cytokine levels was found. Intra-articular IGF-I concentrations significantly correlated with the area of cartilage damage (p = .35, P < .02); the other investigated cytokines failed to show this association. Neither of the determined intra-articular mediators demonstrated statistically significant correlations with subjective knee function or IKDC score. Only intra-articular concentrations of IGF-I and BMP-2 statistically significantly correlated with age; total protein content was negatively associated with body mass index (P < .05). In smokers, synovial expression of total protein content, IGF-I, and bFGF was significantly diminished compared to nonsmokers (P < .05).

Conclusion: Insulin-like growth factor-I is present in knees with circumscribed cartilage lesions in a size-dependent manner; IGF-I levels correlated with indicators of pain perception; smoking negatively influenced synovial cytokine expression related to cartilage metabolism, but pain perception was not altered.

Keywords: prospective; clinical trial; intra-articular; cytokine; cartilage repair; BMP-2; BMP-7; IL-1β; aggrecan; bFGF; IGF-I; pain; smoking
transfer the data collected in context of progressive OA; here, pain perception and transmission originate from release of inflammatory mediators as interleukins, prostanoids, kinins, chemokines, and substance P. However, data collected so far indicate that these candidates play a subordinate role in the pathophysiology of circumscribed cartilage lesions (ie, interleukin [IL]-1β was not associated with the size or presence of smaller cartilage defects in the knee, but was upregulated after cartilage-regenerating surgery such as ACI and microfracturing). Both methods are regarded as established treatment options with documented success in prevention of OA development. Therefore, we recruited a population of patients who had undergone one of these procedures and collected lavage fluids of their knee joints to analyze the cytokine expression. After publishing the data about intra-articular cytokine expressions, the additionally evaluated parameters of knee function and pain sensation were now analyzed. Correlations of cytokine levels with the clinical data were used for identification of mediators for pain perception. Cytokines known for their decisive influence on cartilage regeneration were of special interest, because some data suggest a defect size-dependent expression of IGF-1 or basic fibroblast growth factor (bFGF). Aggrecan was constitutively expressed in knee joints; bone morphogenetic protein (BMP)-2 seemed to play an important role in surgically induced cartilage repair because synovial expression correlated with the clinical outcome. Mediator expression in knee joints is not only influenced by the cartilage defect as the leading pathologic origin. Many other factors as epidemiologic parameters are known to play a role. Therefore, the influence of age, body mass index (BMI), and smoking behavior were also analyzed during this study. Data about the influence of smoking on the progress of RA (rheumatoid arthritis) or OA (osteoarthritis) are limited, but suggest that cigarette smoking and exposure to TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) enhances RA-related inflammatory processes because of tumor necrosis factor (TNF)-α-induced enhanced AhR (aryl hydrocarbon receptor) expression. It further could be shown that smoking impairs the ability for bone marrow lesions to resolve. Age-dependent cytokine expression has been suggested by several studies (ie, for transforming growth factor [TGF]-β or MMPs [matrix metalloproteinases]). Based on mainly animal experiments. Studies addressing age-dependent expression of cartilage-specific cytokines such as IGF-1 or bFGF in humans are rare and indicate that some mediators of cartilage metabolism are expressed in an age-dependent manner. Obesity has been identified as one of the major risk factors for development of OA in the knee and hip. This is not only caused by the mechanical overload of the joint but also by a changed cytokine profile. The biochemical reactions in obese people in the course of OA show certain characteristics that accelerate destruction of the joints. Therefore, it seems obvious that synovial expression of key mediators of cartilage metabolism may also be changed, dependent on BMI.

Taking these thoughts together, this study was undertaken to elucidate the possible role of intra-articular cartilage-specific cytokines in pain perception under consideration of the influence of age, BMI, and smoking behavior. Interleukin-1β, an important inflammatory cytokine with proven effect in OA-driven pain development, and the mediators known for their decisive roles in cartilage metabolism (BMP-2, BMP-7, bFGF, and IGF-1) were included in the study. Furthermore, aggrecan and the total protein content as parameters of cartilage turnover were analyzed.

MATERIALS AND METHODS

Study Design

The study was performed as previously described. Briefly, during a 1-year period (August 2006–September 2007), 47 patients were enrolled in a prospective clinical trial. Selection of patients followed the criteria as defined below.

Inclusion criteria were performance of an arthroscopy of the knee joint, patients in the control group had no cartilage lesion on MRI and diagnostic arthroscopy, patients undergoing microfracturing or ACI had full-thickness cartilage lesions graded 3 and 4 according to International Cartilage Repair Society (ICRS) classification of various size, agreement to participate in the study, and age >17 years and <66 years.

Exclusion criteria were alcohol or drug abuse, mental retardation with incapability to complete the necessary self-reports, joint effusion >30 mL, persistent knee instability, and infection.

The study was approved by the ethical board of the University of Freiburg (AN-EK-FRBG-335/08, study number DRKS00000365 and UKF00122). Informed consent was obtained from every individual included in the study. Although data of the presented study were published previously, data regarding pain perception, BMI, and smoking behavior have not been analyzed and made public before. The results of the previously published data of the same study were summarized in the introduction. All parameters associated with patient status and history were prospectively collected.

Operation Protocols

The ACI surgical technique has been well defined in numerous publications. In all patients, a matrix-associated (Chondro-Gide, Geistlich Biomaterials, Wolhusen, Switzerland) technique for chondrocyte fixation was used. Microfractures were generated with specially bent awls (Chondro-Gide, Arthrex, Karlsfeld, Germany) by creating V-shaped perforation holes with a diameter of 1.5 to 2 mm at a distance of 3 mm (3 or 4 holes/cm²). The applied kind of cartilage surgery was chosen depending on defect size and depth, as previously published. Briefly, only full-thickness cartilage defects correlating with grade 3 (down to but not through the subchondral bone) or grade 4 (subchondral bone is exposed and ruptured) according to ICRS classification were surgically treated. Smaller lesions (<2.5 cm²) were treated by microfracturing and larger defects underwent ACI; both methods were used for lesions between 2.5 and 4 cm².
Specimen Collection

Synovial lavage fluids of knee joints of patients undergoing surgery were intraoperatively collected. Before starting the procedure, 20 mL of sterile physiologic saline was instilled into the joint cavity. The saline was mixed within the joint by repeated passive flexion-extension and repeated manipulation of the supra- and infrapatellar regions, and then was aspirated as described by Geborek et al. This method has been successfully used by a variety of other groups. The total volume aspirated was recorded. Specimens were centrifuged to separate the cells and then stored frozen at -80°C until analyzed.

Characterization of Patients

In 42 patients, the cartilage defects were treated by microfracturing (19 patients) or by ACI (23 patients). The average age of the patients with cartilage lesions was 42 ± 10 years and the gender distribution was equal (21:21). Five patients undergoing a diagnostic arthroscopy for unspecific knee complaints had no cartilage lesion and initially served as a control group. The average age of the control group was 30 ± 12 years; in this group, the gender distribution of male to female was 2:3. Patients of the control group were only included in the correlation studies where appropriate and were indicated by the number of individuals included in the calculation (n), ie, when analyzing the correlations between intra-articular cytokines and BMI; they did not serve as controls for comparisons. The BMI of the patients with cartilage lesions was 26.9 ± 3.5; the BMI of the control group was 25.0 ± 3.74. For clinical evaluation, the International Knee Documentation Committee (IKDC) score, personal evaluation of knee function by visual analog scales (VAS), and VAS evaluation of knee pain strength and frequency were used. Data were obtained directly before operation. Radiographs of all 42 patients with cartilage defects were evaluated for the Kellgren and Lawrence score; standing radiographs were additionally evaluated for leg alignment. In all cases, the performing surgeon identified the cartilage-regenerating surgery as the main cause for the intervention, but in 19 cases additional operative measures were necessary. Cartilage repair was supplemented 10 times by an arthroscopic partial meniscus resection, 6 times by soft tissue patella balancing measures as a lateral release, 2 times by an intercondylar notchplasty, and 3 times by correction of leg malalignment by an open-wedge osteotomy (some knees had multiple procedures).

Grading of Cartilage Lesion

The chondral damage was graded from 0 to 4 based on the ICRS classification. Grade 0 represents normal articular cartilage and grade 1 shows superficial lesions as soft indentation and/or superficial fissures and cracks. A grade 2 defect is a partial-thickness defect; it features lesions extending down to less than 50% of cartilage depth. With grade 3 defects, there are cartilage defects extending down to more than 50% of cartilage depth as well as down to the calcified layer, and down to but not through the subchondral bone. Blisters are included in this grade. In grade 4 injuries, the subchondral bone is exposed and ruptured. The total area of chondral defect per patient was calculated by adding the regions with grade 3 and grade 4 lesions. According to this standardized choice of treatment, the average defect sizes were 3.4 ± 2.0 cm² in case of microfracturing and 6.1 ± 2.8 cm² in case of ACI (P < .001).

Enzyme-Linked Immunosorbent Assays for BMP-2, BMP-7, bFGF, IGF-I, IL-1β, Aggrecan, and Bicinchoninic Acid Protein Assay

To measure concentrations of the indicated proteins, commercially available enzyme-linked immunosorbent assay (ELISA) kits provided by R&D Systems (Wiesbaden-Nordenstadt, Germany) for BMP-2, BMP-7, bFGF, IGF-I, and IL-1β and BioSource (BioSource Deutschland GmbH, Solingen, Germany) for Aggrecan were used according to the manufacturers' instructions. Briefly, the assay employs the quantitative sandwich enzyme immunoassay technique. A specific monoclonal antibody was precoated onto a microplate. Supernatants were applied to the wells and, after washing, an HRP (horseradish peroxidase)-conjugated specific antibody was added to the wells. After the next wash, color development was proportional to protein concentration and was calculated by comparison with a standard. A colorimetric method was used to quantify total protein amount in the lavage fluids. The bicinchoninic acid (BCA) assay was available in kit form from Pierce (Rockford, Illinois) and was used according to the manufacturers' instructions.

Statistics

All values were expressed as mean ± standard deviation. Data sets were examined with 1- and 2-way analysis of variance and individual group means of protein or cytokine concentrations were then compared with the unpaired Student t test, in case of unequal variances (F test) the Aspin-Welch test, in case of unequal variances (F test) the Student's t test has been applied. The power for comparing 2 means was calculated for each individual comparison assuming a 2-sided confidence interval of 95%. Individual group means of scores were compared with the Wilcoxon rank-sum test. Normal probability plots were done on all data sets and correlation determined by either calculating the Pearson or the Spearman's coefficient depending on distribution. Statistical significance was defined when P < .05.

RESULTS

Correlation of Pain Strength and Frequency With Intra-articular Cytokine Concentrations

Pain strength showed a highly significant association with intra-articular IGF-I levels: corrected for age, r = -0.48, n = 49, P = .002; Figure 1), but no correlation with synovial...
Concentrations of bFGF \( p = .07, n = 42, P = .63 \), IL-1β \( p = .12, n = 42, P = .46 \), BMP-2 \( p = -.22, n = 42, P = .16 \), and BMP-7 \( p = .12, n = 42, P = .44 \). Although pain strength and frequency demonstrated a statistically significant relationship (corrected for ties, \( p = .51, n = 42, P = .001 \); Figure 2), no substantial association between pain frequency and any of the examined cytokine levels was found (Table 1).

Correlation of Defect Area, BMI, Subjective Knee Function, and Age With Intra-articular Cytokine Concentrations

Intra-articular IGF-I concentrations statistically significantly correlated with the area of cartilage damage (corrected for ties, \( p = .35, n = 47, P = .018 \); Figure 3); the other investigated cytokines failed to show this association (Table 2). The subgroup analysis showed better correlations in patients with smaller cartilage lesions undergoing microfracturing \( n = 19, p = .46, P = .0244 \) compared with the group with larger defects treated by ACI \( n = 23, p = .18, P = .2016 \). None of the determined intra-articular mediators demonstrated statistically significant correlations with subjective knee function evaluated by a VAS \( n = 42; \) Table 3). The total protein content in the knee lavages negatively correlated with BMI \( p = -.330, n = 47, P = .025 \); expression of all other investigated separate proteins did not show any statistically significant correlation with BMI \( n = 47; \) Table 3). Furthermore, the association between age and synovial cytokine levels was analyzed. Intra-articular concentrations of IGF-I \( p = .365, n = 47, P = .012 \) and BMP-2 \( p = .385, n = 47, P = .044 \) were statistically significantly correlated with age; the older the patients, the more IGF-I or BMP-2 was detected. All other cytokines did not show a statistically significant association with the age of the patient.
Overview of Correlation of Age With Cartilage Damage and Cytokine Expression

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>( p )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>0.175</td>
<td>0.904</td>
</tr>
<tr>
<td>Aggrecan</td>
<td>0.104</td>
<td>0.500</td>
</tr>
<tr>
<td>IL-1( \beta )</td>
<td>0.155</td>
<td>0.500</td>
</tr>
<tr>
<td>bFGF</td>
<td>0.008</td>
<td>0.935</td>
</tr>
<tr>
<td>IGF-I</td>
<td>0.013</td>
<td>0.604</td>
</tr>
<tr>
<td>BMP-2</td>
<td>0.142</td>
<td>0.693</td>
</tr>
<tr>
<td>BMP-7</td>
<td>0.085</td>
<td>0.904</td>
</tr>
</tbody>
</table>

*aIL, interleukin; bFGF, basic fibroblast growth factor; IGF, insulin-like growth factor; BMP, bone morphogenetic protein.

**Statistically significant value with correlation coefficient.

Comparison of Pain Perception (VAS) and Intra-articular Cytokine Levels in Smokers and Nonsmokers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nonsmokers (n = 27)</th>
<th>Smokers (n = 15)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS, VAS</td>
<td>9.63 ± 11.76</td>
<td>6.13 ± 2.42</td>
<td>0.375</td>
</tr>
<tr>
<td>PP, VAS</td>
<td>7.41 ± 2.061</td>
<td>8.00 ± 2.27</td>
<td>0.359</td>
</tr>
<tr>
<td>IKDC</td>
<td>38.76 ± 11.97</td>
<td>23.61 ± 15.15</td>
<td>0.016</td>
</tr>
<tr>
<td>Protein</td>
<td>1.23 ± 14.38</td>
<td>0.81 ± 14.38</td>
<td>0.12</td>
</tr>
<tr>
<td>IL-1( \beta )</td>
<td>5.43 ± 6.21</td>
<td>2.37 ± 5.83</td>
<td>0.067</td>
</tr>
<tr>
<td>bFGF</td>
<td>30.12 ± 27.81</td>
<td>18.71 ± 7.07</td>
<td>0.045</td>
</tr>
<tr>
<td>IGF-I</td>
<td>36.59 ± 28.29</td>
<td>20.71 ± 7.07</td>
<td>0.042</td>
</tr>
<tr>
<td>BMP-2</td>
<td>19.47 ± 17.56</td>
<td>12.71 ± 15.76</td>
<td>0.052</td>
</tr>
<tr>
<td>BMP-7</td>
<td>8.06 ± 24.36</td>
<td>9.47 ± 24.80</td>
<td>0.857</td>
</tr>
</tbody>
</table>

*aVAS, visual analog scale; PS, pain strength; FF, pain frequency; IKDC, International Knee Documentation Committee; IL, interleukin; bFGF, basic fibroblast growth factor; IGF, insulin-like growth factor; BMP, bone morphogenetic protein.

**Wilcoxon rank-sum test (Mann-Whitney U test) for unequal data.

***P values for unequal variances (Aspin-Welch).

**Statistically significant.

Influence of Smoking Behavior

Because a statistically significant association between age and synovial cytokine levels has been demonstrated, age of smokers (39.8 ± 6.9 years, n = 27) and nonsmokers (42.7 ± 11.0 years, n = 27) was compared and did not show a statistically significant difference (\( P = 0.335 \); power, 73.31%). Gender comparison showed in the group of smokers a distribution of 6 men and 9 women compared with the group of nonsmokers with 15 men and 12 women. This gender distribution was not statistically different between the groups (\( P = 0.335 \); power, 73.31%). The group of nonsmokers had an average BMI of 25.77 ± 2.36 (n = 27), which was higher than the BMI in the group of smokers with 23.81 ± 2.94 (n = 15) but not statistically different (\( P = 0.0726 \); power, 73.31%). There was no difference in pain perception in both groups according to strength and frequency, and no difference in IKDC score (6.68 ± 1.76 vs 6.13 ± 2.42; Table 4). Synovial total protein content, IGF-I (\( P = 0.033 \); power, 62.1% and 62.3%), and bFGF levels (\( P = 0.042 \); power, 64.63%) were decreased in the subgroup of smokers (Table 4). There was no correlation of the amount of pack years (14.1 ± 10.82 years; minimum 4.5, maximum 45) with total protein content (\( P = 0.2576 \), IGF-I (\( P = 0.2205 \)), or bFGF (\( P = 0.0745 \)).

DISCUSSION

Pain Perception

Perception of pain is a decisive parameter when evaluating knee function and quality of life. Mediators and pathogenesis of pain development following circumscribed...
Cateors of pain perception. This could not be demonstrated in patients with knee OA has been demonstrated. A relationship between subchondral bone plate exposure and prevalent and incident knee pain has been demonstrated. This might be explained by the positive immunoreactivity of substance P, cyclooxygenase (COX)-2, TNF-α, and Tuj1 (neuron-specific class III β-tubulin) in the subchondral bone of affected knee compartments. The relatively immediate reduction in pain obtained by TKA (total knee arthroplasty) might account for the involvement of the subchondral bone in knee pain because most of the affected subchondral plate is excised in TKA. These data are supported by our finding that KLS is correlated with pain strength. The role of bone marrow lesions in the development of pain still remains doubtful, but it has been shown that subchondral bone marrow edema at the time of treatment represents a negative prognostic factor for early outcome after ACL. Although pathophysiology of pain with effect on the subchondral bone layer has a common basis in manifest and early onset OA, the biochemical transmission appears to be different. Whereas interleukins are considered not only as major factors in development of inflammation but also as key transmitters of pain perception in advanced OA, in our study IL-1β did not correlate with any parameter of pain sensation nor with defect area or other confounding parameters such as age or BMI. There are only a few studies that address the issue of synovial or serum expression of cartilage-specific markers in patients with early-stage knee OA and limited synovitis in association with outcome and pain perception. In addition to our data about IGF-I, it has been shown that chondroitin 6-sulfate (C6S), chondroitin 4-sulfate (C4S), keratan sulfate (KS), and tenascin-C (TN-C), cytokine receptor-like factor 1 (downstream of TGF-β), or increased serum COMP (cartilage oligomeric matrix protein) levels play a role as indicators or mediators in this stage of disease development. Because of its observational character, the study does not allow drawing any conclusions of how IGF-I is acting in detail, and it also remains unclear what molecular mechanisms are behind the observed association between synovial IGF-I levels and pain perception. But it is likely that underlying mechanisms are similar to the observed effects in diabetic neuropathy.

Smoking, Age, and Body Mass Index

Smoking should not only be considered a general cardiopulmonary risk factor, but is also associated with poorer results after ACL. The biochemical mechanisms behind this phenomenon are not completely understood, but it has been shown that nicotine inhibits expression of a wide range of cytokines and proteins of the extracellular cartilage matrix as type I and type II collagen, BMP-2, 4, and -6, bFGF, and vascular endothelial growth factor. These results of animal experiments were confirmed in the present study. In patients undergoing cartilage-regenerating surgery, a significant decrease in total protein

Figure 4. Frequency distribution of leg alignments. In cases of 2 outliers with varus malalignment between 9° and 10°, cartilage regeneration was accompanied by a correcting open-wedge osteotomy. Negative values indicate valgus and positive values indicate varus malalignment.

cartilage damage are not yet fully understood. In this study, it could be demonstrated that IGF-I is expressed in knees with circumscibed cartilage lesions in a size-dependent manner; these IGF-I levels correlate with indicators of pain perception. This could not be demonstrated for the other investigated proteins: hFGF, aggrecan, IL-1β, or BMP-2 and BMP-7. The role of IGF-I in diabetic polyneuropathy that is associated with decreased pain perception has been very well defined. It has been shown that IGF activity is reduced in diabetic neural tissues, that conduction velocity is impaired in the diabetic spinal cord, that replacement therapy with IGF may prevent neuropathy in diabetic nerves, and that IGFs can prevent diabetic neuropathy. The physiologic reasoning behind these effects seems to lie in IGF-induced amelioration of nerve degeneration that has also been suggested for other neurotrophic factors, such as NGF (nerve growth factor) or NT-3 (neurotrophin 3), and was demonstrated in both in vitro and in animal models of neuropathies. The regenerating effects of IGF-I seem to be limited to the peripheral nervous system, because in an experimental animal model for diabetic neuropathy the growth factor was able to reverse the reduced thermal sensitivity and the peripheral nerve conduction velocity but did not reverse changes in the CNS (central nervous system). For patients with circumscibed cartilage lesions, we would conclude that IGF-I shows increased synovial levels as a key regulator of cartilage repair and metabolism, but also exerts abilities as a neurotrophic factor increasing pain perception. It remains unclear to what extent other intra-articular pathologic changes contribute to IGF expression.

The mechanisms of pain origination in manifest OA are better understood and investigated than in cases of circumscibed cartilage defects that may be considered as early-onset OA. Advanced cartilage degeneration seems to be associated with augmented chemically induced joint pain, because nociceptors in osteoarthritic joints are more sensitive to inflammatory mediators than in normal joints. A specific role in pain origination seems to be attributed to the subchondral bone. A relationship between subchondral bone plate exposure and prevalent and incident knee pain in patients with knee OA has been demonstrated. This might be explained by the positive immunoreactivity of substance P, cyclooxygenase (COX)-2, TNF-α, and Tuj1 (neuron-specific class III β-tubulin) in the subchondral bone of affected knee compartments. The relatively immediate reduction in pain obtained by TKA (total knee arthroplasty) might account for the involvement of the subchondral bone in knee pain because most of the affected subchondral plate is excised in TKA. These data are supported by our finding that KLS is correlated with pain strength. The role of bone marrow lesions in the development of pain still remains doubtful, but it has been shown that subchondral bone marrow edema at the time of treatment represents a negative prognostic factor for early outcome after ACL. Although pathophysiology of pain with effect on the subchondral bone layer has a common basis in manifest and early onset OA, the biochemical transmission appears to be different. Whereas interleukins are considered not only as major factors in development of inflammation but also as key transmitters of pain perception in advanced OA, in our study IL-1β did not correlate with any parameter of pain sensation nor with defect area or other confounding parameters such as age or BMI. There are only a few studies that address the issue of synovial or serum expression of cartilage-specific markers in patients with early-stage knee OA and limited synovitis in association with outcome and pain perception. In addition to our data about IGF-I, it has been shown that chondroitin 6-sulfate (C6S), chondroitin 4-sulfate (C4S), keratan sulfate (KS), and tenascin-C (TN-C), cytokine receptor-like factor 1 (downstream of TGF-β), or increased serum COMP (cartilage oligomeric matrix protein) levels play a role as indicators or mediators in this stage of disease development. Because of its observational character, the study does not allow drawing any conclusions of how IGF-I is acting in detail, and it also remains unclear what molecular mechanisms are behind the observed association between synovial IGF-I levels and pain perception. But it is likely that underlying mechanisms are similar to the observed effects in diabetic neuropathy.

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Insulin growth factor-I is expressed in knees with circumferential cartilage lesions in a size-dependent manner; synovial levels correlate with indicators of pain perception. This indicates a role for IGF-I in cartilage repair and amelioration of nerve tissue formation with increased pain sensation. This might explain the fact that IGF-I levels negatively correlate with clinical knee scores in patients with larger defects as previously published, because increased pain perception leads to decreased functional score values. Smoking leads to reduction of bFGF and IGF-I-expression, which might be related to worse cartilage repair capabilities in smokers. Age influences synovial levels of BMP-2 and IGF-I, which appear to be in line with age-related alteration of cytokine profiles predisposing for degenerative diseases.

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