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Increased BMP expression in arthrofibrosis after TKA

Tilman Pfitzner · Sven Geissler · Georg Duda · Carsten Perka · Georg Matziolis

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Abstract
Purpose Because of the multiple possible aetiologies of painful total knee arthroplasty (TKA), the diagnosis and treatment of such patients are challenging. In a considerable number of patients, an intraarticular pathology is present, although not verifiable with clinical and diagnostic imaging techniques as in cases of primary arthrofibrosis. In these patients, the differentiation between intra- and extraarticular causes of pain remains difficult. Until now, little attention has been paid to changes of the synovial fluid and tissue in these knees. The objective of this study was to analyse the changes of the synovial environment in patients suffering from arthrofibrosis after TKA in comparison with knees with referred pain suffering from hip arthritis. The changes of the synovial environment probably provide additional diagnostic information to verify an intraarticular pathology.
Methods The synovial fluid of 10 consecutive knees in 10 patients presenting with a primary arthrofibrosis after TKA without signs of infection, instability, malalignment, or loosening was analysed and compared to the synovial fluid of 10 knees with referred pain serving as controls. The BMP-2 concentration was measured in the synovial fluid, and the presence of cytokines leading to an overexpression of BMP-2 was detected by measuring the change of BMP-2 expression in a synoviocyte cell line following exposing to the synovial fluid of the patients.
Results The concentration of BMP-2 in the synovial fluid was significantly higher in arthrofibrotic TKA knees (24.3 ± 6.9 pg/mL), compared with the control group 5.9 ± 4.8 pg/mL ($P < 0.001$). Corresponding to this finding, BMP-2 expression in synoviocytes was upregulated 11.5-fold ($P < 0.05$) by synovial fluid of patients suffering from arthrofibrosis after TKA, compared with the control group with referred pain.
Conclusion BMP-2 is overexpressed and its concentrations are consequently higher in patients suffering from arthrofibrosis after TKA. The synovial BMP-2 concentration may be a potential marker for differentiating between intra- and extraarticular causes of pain.
Level of evidence II.

Keywords Total knee arthroplasty · Arthrofibrosis · Inflammation · BMP-2

T. Pfitzner (✉) · C. Perka · G. Matziolis
Orthopaedic Department, Center for Musculoskeletal Surgery, Charité—University Medicine Berlin, Charitеplatz 1, 10117 Berlin, Germany
e-mail: tilman.pfitzner@charite.de

S. Geissler · G. Duda
Julius Wolff Institute, Charité—University Medicine Berlin, Berlin, Germany

Introduction

The past decades have brought continuous improvement in total knee arthroplasty (TKA). More sophisticated surgical techniques as well as new implant designs have led to more satisfactory outcomes [4, 26, 36]. However, the diagnosis of painful TKA continues to be a challenge, due to its multiple possible origins [43, 44]. The diagnostic algorithm includes different non-invasive and invasive examinations of the knee joint (e.g. X-ray, computed tomography, aspiration, arthroscopy). Therefore, causes of pain not related to the knee joint should be excluded first. The most common causes are spinal stenosis, coxalgia, neuroma, vascular diseases, and psychosomatic diseases [1, 6, 9, 13, 21, 24,

25, 27, 32, 33, 38]. Despite a knowledge of biological and mechanical causes of intraarticular cause of pain (e.g. infection, instability, loosening, malalignment, arthrofibrosis, allergy), the origin sometimes remains difficult to determine with clinical and diagnostic imaging techniques [44]. Especially the diagnosis of primary arthrofibrosis is due to its indistinct aetiology often confirmed only clinically. Although the differentiation between extra- and intraarticular causes of knee pain is crucial, appropriate diagnostic tools have not been available up to now. Treatment options of primary arthrofibrosis after TKA are physical therapy, manipulation under anaesthesia, arthroscopy or open arthrolysis [2, 10, 18]. These procedures mostly achieve an improvement in range of motion, but randomized studies regarding the outcome are missing [10, 18].

Transforming growth factor-ß (TGF-ß) plays a key role in the pathogenesis of arthrofibrosis due to an increased inflammatory reaction [11, 12, 48]. Bone morphogenetic protein 2 (BMP-2) is a low molecular weight glycoprotein that belongs to the TGF-β protein superfamily. It has versatile functions, like skeletal organogenesis, osteoinduction, and regeneration [35]. Of particular relevance to the present study hypothesis, BMP-2 is also known to be responsible for increased inflammatory tissue reactions [37, 50]. Several clinical reports have described excessive inflammatory reactions with long-lasting pain after vertebral fusion and application of BMP-2 [14, 30, 37]. The close connection between chronic painful inflammation and changes of the synovial tissue and fluid is well accepted in the pathogenesis of osteoarthritis and rheumatoid arthritis [16, 23, 42, 47].

In contrast to this, extraarticular diseases do not alter the synovial environment of the knee joint.

It seems plausible that changes in the synovial fluid identified as being typical for arthrofibrosis after TKA would be of diagnostic value. The hypothesis of this study was that patients suffering from primary arthrofibrosis after TKA present increased levels of inflammatory procytokines and cytokines in the synovial fluid.

Materials and methods

Patients with a painful knee of intra- or extraarticular origins were included in this comparative study. The study protocol was approved by the institutional review board, and all patients gave their informed consent. Clinical patient data were documented for each patient, including age, gender, side and time since implantation.

There is no consensus in the literature for a consistent definition of arthrofibrosis after TKA [39]. In our study, arthrofibrosis was defined as painful limitation of range of motion less than 90° including an extension deficit of more than 10° according to the classification of Yercan et al. [49]. Regarding pain inclusion criteria were persistent pain of more than 6 months' duration after primary TKA and intensity of rest pain >5 on a visual analogue scale (VAS) and pain >7 under weight-bearing conditions on the VAS.

All knees showing signs of infection, loosening, instability, impingement, or malalignment were excluded.

Patients awaiting total hip replacement and with knee pain related to their hip pathology for more than 6 months were included in the group with an extraarticular cause of pain (group B). All patients in group B underwent radiographic examination of the involved knee. Patients suffering from osteoarthritis of this joint were excluded (defined as radiographic changes exceeding stadium 1 according to Kellgren and Lawrence).

Aspiration was performed in all knees once during the study and a minimum of 5 mL of synovial fluid was immediately cryoconserved and stored at −20°C until examination. The concentration of bone morphogenetic protein (BMP-2), as part of the TGF-β protein superfamily that plays a key role in the pathogenesis of arthrofibrosis [11, 12, 48], was measured with an ELISA.

BMP-2 ELISA

The concentration of BMP-2 was analysed in the synovial fluid of all knees with the "Quantikine BMP-2 Immunoassay Kit" according to the manufacturer's protocol (R&D systems, Minnesota, USA). This assay works with a quantitative sandwich enzyme immunoassay technique. Extinction was measured in a microplate reader at a wavelength of 450 nm.

Gene expression analysis (rtPCR)

In order to detect all cytokines maintaining a vicious circle of inflammation, resulting in a change of BMP-2 concentration in the synovial fluid, a part of the aspirates was added to a synovial cell line and the change of BMP-2 mRNA expression pattern was determined.

Cell culture was done with immortalized human synovial cells (SW-982) deriving from a synovial sarcoma purchased from the American Type Culture Collection (Bethesda, MD) [8]. The synovial cells were cultured with Dulbecco's modified Eagle's medium (DMEM) (Gibco, Grand Island, NY) supplemented with 10% foetal calf serum (FCS) (Biochrom AG, Berlin) and 100 U/mL penicillin plus 100 lg/mL streptomycin (Expansion medium, EM). Cells were passaged at 70–80% confluence, and passages 10–15 were used for experiments [22]. Cells were incubated in a humidified incubator at 37°C and 5% CO_2. For the experiments, 1.7×10^5 cells were seeded in

25 cm^2 plastic flasks. After cell adherence, 2 mL of synovial fluid were added to the culture flasks and incubated for 48 h. The cells were then washed and immediately harvested for gene expression analysis.

Total RNA was isolated with the "RNeasy Mini Kit" (Qiagen, Maryland, USA). Digestion of residual amounts of DNA was performed with an additional step in the isolation procedure with the "RNAse-free DNAse Set" (Qiagen, Maryland, USA). One microgram of RNA of each sample was reversed transcribed using the "RT^2 First Strand Kit" (SA Biosciences, Maryland, USA) [34]. For gene profiling, samples were applied to 384-well "RT^2-Profiler PCR Array" plates for human inflammatory response and autoimmunity (SA Biosciences, Maryland, USA). PCR was performed in an Applied Biosystems ABI 7900 HT fast real-time PCR system with a 384-well block. A standard curve and an end-time dissociation curve were done for each plate, baseline and threshold cycles being detected automatically.

For comparison of the data between the plates, a baseline of 0.3 and threshold cycles from 2 to 10 were defined. Data were analysed by using the ΔΔ-CT method [29]. This mathematical method relates the PCR signal of the target gene (BMP-2) of group A to the signal of the target gene of group B. This allows a relative comparison of both groups.

The ELISA and rtPCR measurements are well-established methods and were performed according to the manufacturers' instructions, so that neither a test–retest reliability nor a test of inter-observer variation was determined.

Statistical analysis

Descriptive statistics (mean, minimum, maximum, and standard deviations) were calculated from the measured data.

Statistical analysis of the PCR data between the samples was performed with the ΔΔ-CT method [29]. The Mann–Whitney *U* test was used for nonparametrically unmatched correlation analysis between the groups, and the Wilcoxon Test for nonparametrically matched samples. $P = 0.05$ was defined as the level of significance.

Results

The mean age of the patients was comparable between group A (70.2 ± 9.1 years) and group B (66.8 ± 12.3 years, n.s.). Five men and 5 women patients were included in each group. The ratio between left and right knees was 8/2 in group A and 7/3 in group B. The average time since implantation of the TKA in group A was 23 ± 16 months.

BMP-2 ELISA

The BMP-2 concentration in the synovial fluid of group A knees was 24.3 ± 6.9 pg/mL. In contrast, group B knees presented a significantly lower BMP-2 concentration of just 5.9 ± 4.9 pg/mL ($P < 0.001$) (Fig. 1).

Gene expression analysis (rt-PCR)

The Ct value of BMP-2 of the native synoviocytes before addition of synovial fluid was 30.0 ± 4.2. In contrast, the Ct value was significantly reduced in group A to 27.7 ± 3.9 ($P < 0.05$). The synovial fluid of group B knees did not change the Ct value (31.4 ± 1.0). These values correspond to a 11.5 ± 0.1-fold expression of BMP-2 in group A knees compared with group B knees ($P < 0.05$) (Fig. 2).

Discussion

The most important finding of the present study was that BMP-2 concentration in the synovial fluid is significantly increased in patients suffering from arthrofibrosis after TKA, compared to patients with knee pain related to extraarticular factors. It could also be shown that the addition of synovial fluid to a synoviocyte cell line led to increased BMP-2 mRNA expression. This finding demonstrates that the increased BMP-2 concentration in arthrofibrotic knees after TKA resulted from cytokines in the synovial fluid following changes of the synovial tissue.

The aetiology of arthrofibrosis is still mostly indistinct. Factors like comorbidities, preoperative knee function, molecular factors (e.g. mast cell proliferation), surgical approach, and ineffective postoperative pain management are described [11, 20, 28, 39]. A pathologic immune response with the following chronic inflammation is also discussed [3]. Freeman et al. [12] showed an increased infiltration of inflammatory cells in arthrofibrosis. The

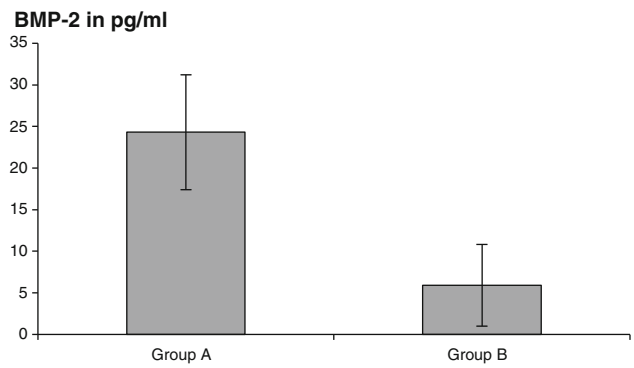

Fig. 1 BMP-2 concentration in ELISA between group A and group B

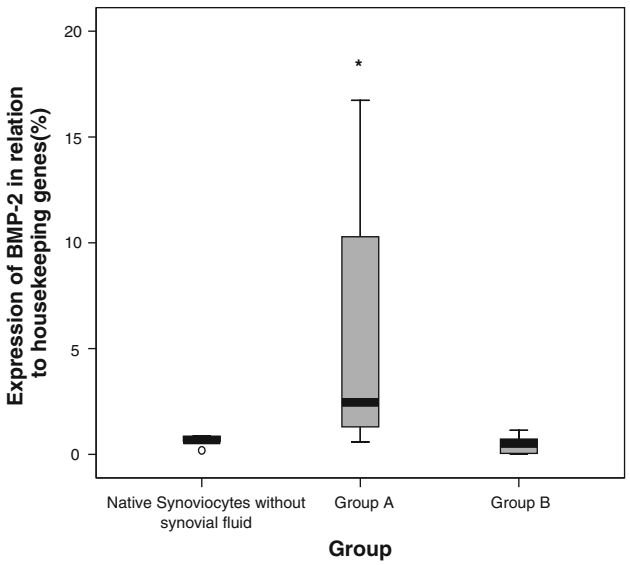

Fig. 2 Expression of BMP-2 in painful TKA compared with healthy knees and native synovial cells

normal resolution of the inflammatory reaction in tissue repair fails resulting in a persistent inflammation of the synovial tissue. Furthermore, a dysregulation on cytokine level seems to be present. Beside inflammatory cytokines (TNF-α, IL-1 and IL-6), there is an upregulation of TGF-β- and platelet-derived growth factor (PDGF), triggering an irreversible tissue fibrosis via the transformation of fibroblasts [48, 51].

BMP-2 is part of the same protein superfamily as TGF-β and may therefore be upregulated in arthrofibrosis, too. BMP-2 is an important factor in this multifactorial aetiology, but to our knowledge, it was not described as independent factor in the pathogenesis of arthrofibrosis until now.

Schmal et al. [40] investigated the BMP-2 levels in painful knees with intraarticular cause of pain (cartilage defect) and found even higher levels in comparison with our data that were not correlated to the pain level. This fortifies our hypothesis that increased BMP-2 levels are present in intraarticular causes of pain. Moreover, BMP-2 stimulates the expression of neurofilaments in peripheral nerves [7, 45, 46], which is similar to a treatment with nerve growth factor (NGF) [19]. BMP-2 is also an important cofactor of tumour necrosis factor (TNF-α) in peripheral nerve regeneration and nociception. Together with TNF-α, it stimulates the production of NGF in fibroblasts [17]. Some studies have shown that NGF is expressed in various inflammatory cells and is a potent mediator of pain and inflammation [5, 31, 52]. The authors concluded that the NGF system plays a key role in chronic and inflammatory pain response [5]. Upregulation of BMP-2 may therefore contribute to the pathogenesis of chronic pain via NGF.

This study is limited by the fact that the knee joints in the group of extraarticular cause of pain were non-replaced and only referred from hip pathology. Another limitation is that no allergy test was performed in the patients of group A. The role of allergy as an evident cause of pain after TKA is still indistinct. Degradation products of metal or acrylic cements are able to interact with the immune system and may induce a delay-type hypersensitivity reaction [15]. But there is still no evidence whether this causes persistent pain and implant failure in these patients [15, 41]. Schuh et al. [41] found a large amount of patients with allergy to implant metal and arthroplasty which were completely asymptomatic.

Conclusion

The synovial BMP-2 concentration could be a new and helpful tool in the differential diagnosis of painful total knee arthroplasty pointing the focus of further investigations on primary arthrofibrosis.

Conflict of interest The authors declare that there is no conflict of interest.

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