

Osteoarthritis and Cartilage



Surgical reconstruction of ruptured anterior cruciate ligament prolongs trauma-induced increase of inflammatory cytokines in synovial fluid: an exploratory analysis in the KANON trial

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SUMMARY

Objective: Prospectively monitor how treatment of acutely ruptured anterior cruciate ligament (ACL) affects biomarkers of inflammation and proteolytic degradation over 5 years.

Design: We studied 119 subjects with acute ACL injury from the randomized controlled knee anterior cruciate ligament, non-surgical versus surgical treatment (KANON)-trial (Clinical trial ISRCTN 84752559) who had synovial fluid, serum and urine samples available from at least two out of six visits over 5 years after acute ACL rupture. All subjects followed a similar rehabilitation protocol where, according to randomization, 60 also had early ACL reconstruction and 59 had the option to undergo a delayed ACL reconstruction if needed. Interleukin (IL)-6, IL-8, IL-10, interferon-gamma (IFN γ), tumor necrosis factor (TNF), amino acids alanine, arginine, glycine, serine (ARGS)-aggrecan, C-terminal crosslinking telopeptide type II collagen (CTX-II) and N-terminal crosslinking telopeptide type I collagen (NTX-I) were quantified by enzyme-linked immunosorbent assays (ELISA).

Results: Subjects randomized to early ACL reconstruction had higher cytokine concentrations in index knee synovial fluid at 4 months (IL-6, IL-8, IL-10, TNF), 8 months (IL-6 and TNF) and at 5 years (IFN γ) compared to those randomized to optional delayed reconstruction. Those that underwent delayed ACL reconstruction within 5 years (30 subjects), had higher synovial fluid concentrations of IL-6 at 5 years compared to those treated with rehabilitation alone. No differences between groups were noted for ARGS-aggrecan in synovial fluid and serum or CTX-II and NTX-I in urine over 5 years, neither as randomized nor as treated.

Conclusions: Surgical ACL reconstruction constitutes a second trauma to the acutely injured joint resulting in a prolonged elevation of already high synovial fluid levels of inflammatory cytokines.

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Introduction

Trauma-induced cytokine response after knee injury has a role in the development of posttraumatic osteoarthritis (OA)^{1,2}. The link between pro-inflammatory cytokines and cartilage catabolism through elevation of aggrecanase and matrix metalloprotease activity is well established³. Synovial fluid levels of aggrecanase generated aggrecan amino acids alanine, arginine, glycine, serine (ARGS) neopeptide (ARGS-aggrecan) were shown to associate with radiographic progression of knee OA after meniscus injury, and with worsening in self-reported outcomes of OA in subjects with

previous meniscectomy^{4,5}. In the same meniscectomized subjects similar associations were shown between synovial fluid levels of tumor necrosis factor (TNF), interleukin (IL)-6 and radiographic OA progression, and with worsening in self-reported outcomes of OA⁶. As part of a randomized controlled trial (RCT) comparing outcomes of the treatment strategies of early anterior cruciate ligament (ACL) reconstruction or delayed optional ACL reconstruction in patients with acute ACL injury (the knee anterior cruciate ligament, non-surgical versus surgical treatment [KANON] trial), we reported immediate and prolonged increase in synovial fluid levels of inflammatory cytokines and ARGS-aggrecan and urine levels of CTX-II with subsequent decreasing levels over 5 years after injury⁷. In the present exploratory analysis of this RCT, we extend these findings, showing that surgical ACL reconstruction in the acute post-injury phase represents a second trauma to the injured knee resulting in a prolonged elevation of already high synovial fluid levels of inflammatory cytokines.

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Patients and methods

Subjects and samples

In the KANON trial (ISRCTN 84752559), 121 subjects (26% women, mean age 26 years, SD 4.9) with an acute ACL rupture to a previously un-injured knee, were followed at baseline (0–6 weeks after injury), 2 and 5 years after injury, with additional follow ups at 4, 8 and 12 months for the 63 first included subjects. In addition to a similar structured rehabilitation protocol administered to all patients, 62 subjects were randomized to undergo early ACL reconstruction (performed within 10 weeks after injury) and 59 to the option of having a delayed ACL reconstruction if needed⁸. One subject randomized to early ACL reconstruction did not undergo surgery. After 5 years one additional subject was non-compliant to treatment and one was lost to follow up.

Two patients randomized to early ACL reconstruction (including the subject that did not undergo surgery) had no samples of synovial fluid, blood or urine taken at any of the follow up visits over 5 years. Consequently, 119 out of 121 participants constituted the full analysis set in this 5-year follow up report on biochemical markers (60 randomized to early ACL reconstruction and 59 randomized to optional delayed ACL reconstruction). One of the 119 subjects in the full analysis set was non-compliant to treatment after 5 years and was excluded from the as-treated analysis, leaving 118 subjects in this analysis: early ACL reconstruction ($n = 59$), rehabilitation alone ($n = 29$), and delayed ACL reconstruction ($n = 30$)⁹. Baseline characteristics of the subjects and the number of samples available at each visit are presented in Table I. Further details on these subjects were as published^{8,9}.

Surgeries

Of the 119 study knees, 106 (89%) underwent at least one surgical procedure to the index knee over the 5-year period. In this study, we classified all surgical procedures involving an ACL

reconstruction as “ACL reconstructions” (all performed by arthroscopy and in about 50% also including meniscus surgery); surgeries where no ACL reconstruction was performed were classified as “non-ACL surgeries”. Sixty-nine out of 72 (96%) of the non-ACL surgeries were by arthroscopy and included surgery to the meniscus⁹, synovectomy, resection of plica, cyclops or ligament remnant, notchplasty or diagnostic procedure; three were non-arthroscopic procedures for other reasons (removal of osteosynthesis material or staple, mobilization under anesthesia). Timing of each surgical procedure was accounted for in the analyses (Fig. 1), although without discrimination of the number of procedures to each individual knee.

After 5 years, the number of non-ACL surgeries was almost twice as high in the group randomized to optional delayed ACL reconstruction compared with the early ACL reconstruction group (45 and 27, respectively; Fig. 1A, Table I). For patients treated by the strategy of early ACL reconstruction, frequent concomitant interventions were done in the same surgical session as the early ACL reconstruction; such interventions are accounted for as separate non-ACL surgeries among the patients treated by the strategy of optional delayed ACL reconstruction⁸. For the as treated groups, the number of non-ACL surgeries were 27 in the early ACL reconstruction group, 23 in the rehabilitation alone group, and 22 in the group with delayed ACL reconstructions (Fig. 1B, Table I). Further details on the non-ACL surgeries were as published¹⁰.

Reference subjects and samples

Biomarker levels in samples from a convenience cohort of donors without a history of knee injury or from subjects with non-specific knee symptoms, who were classified as having knees without structural injury or degeneration based on normal findings on clinical examination, arthroscopy and plain radiography, were used as reference. We selected samples from subjects approximately age and sex matched to the study group at baseline (21 samples of synovial fluid, 23 of serum and 45 of urine), with an additional reference group

Table I
Baseline characteristics and sample availability of the study participants

Characteristics	Full analysis set			Groups as treated at 5 years			
	Early ACL reconstruction ($n = 60$)	Optional delayed ACL reconstruction ($n = 59$)	<i>P</i>	Early ACL reconstruction ($n = 59$)	Rehabilitation alone ($n = 29$)	Delayed ACL reconstruction ($n = 30$)	<i>P</i>
Mean age, years (SD)	26.5 (5.1)	25.8 (4.7)	0.45	26.6 (5.1)	26.4 (4.9)	25.2 (4.5)	0.45
Female sex, no. (%)	12 (20)	20 (34)	0.09	12 (20)	9 (31)	11 (37)	0.22
Mean BMI, kg/m ² (SD)	24.4 (3.2)	23.8 (2.6)	0.24	24.5 (3.2)	24.3 (3.1)	23.3 (2.0)	0.20
Availability of synovial fluid, no. (%)							
Baseline	26 (43)	20 (34)	0.29	25 (42)	10 (34)	10 (33)	0.64
4 months	29 (48)	21 (36)	0.16	29 (49)	12 (41)	9 (30)	0.22
8 months	28 (47)	20 (34)	0.16	28 (48)	10 (34)	10 (33)	0.32
1 year	30 (50)	19 (32)	0.049	30 (51)	8 (28)	11 (37)	0.09
2 years	47 (78)	38 (64)	0.09	47 (80)	20 (69)	18 (60)	0.14
5 years	38 (63)	30 (51)	0.17	38 (64)	12 (41)	18 (60)	0.12
Availability of serum & urine, no. (%)							
Baseline	60 (100)	59 (100)	–	59 (100)	29 (100)	30 (100)	–
4 months	34 (57)	30 (51)	0.52	34 (58)	15 (52)	15 (50)	0.75
8 months	34 (57)	29 (49)	0.41	34 (58)	14 (48)	15 (50)	0.65
1 year	34 (57)	29 (49)	0.41	34 (58)	14 (48)	15 (50)	0.65
2 years	60 (100)	59 (100)	–	59 (100)	29 (100)	30 (100)	–
5 years	58 (97)	58 (98)	0.57	57 (97)	28 (97)	30 (100)	0.59
Weeks injury to ACL surgery, median (range)	6 (2, 173)	59 (26, 244)	<0.001	6 (2, 173)	N/a	59 (26, 244)	<0.001
Surgery occasions, no. (mean per knee)*							
ACL surgeries	63 (1.05)	30 (0.51)	<0.001	62 (1.05)	0 (0)	30 (1.00)	<0.001
Non-ACL surgeries	27 (0.45)	45 (0.76)	0.043	27 (0.46)	23 (0.79)	22 (0.73)	0.14
All surgeries	90 (1.50)	75 (1.27)	0.17	89 (1.51)	23 (0.79)	52 (1.73)	<0.001

* Mean per total knees in the group. N/a = not applicable.

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