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Inflammation and post-operative recovery in patients undergoing total knee arthroplasty-secondary analysis of a randomized controlled trial

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SUMMARY

Objective: Reduced function persists for many patients after total knee arthroplasty (TKA). Inflammation is part of osteoarthritis' pathophysiology, and surgery induces a marked inflammatory response. We therefore wanted to explore the role of inflammation in long-term recovery after TKA, and thus conducted this secondary analysis of our randomized controlled trial (RCT) of physical rehabilitation ± progressive strength training (PST). We aimed to investigate whether (1) inflammation is associated with functional performance, knee-extension strength, and knee pain before TKA; (2) PST affects inflammation, and the inflammatory state over time; (3) baseline or surgery-induced inflammation modifies the effect of rehabilitation ± PST on change in 6-min walk test (Δ6MWT); and (4) baseline or surgery-induced inflammation is associated with Δ6MWT following TKA.

Design: In the primary trial report's per-protocol analysis, 72/82 patients were included. Sixty had ≥1 blood sample before and after TKA, and were included in this secondary analysis. Inflammation was measured by interferon γ-inducible protein (IP)-10, soluble urokinase plasminogen activator receptor (suPAR), interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF)-α at baseline; day 1, week 4, 8, and 26 after TKA.

Results: At baseline, suPAR ($P = 006$) was negatively associated with 6MWT. Neither baseline nor surgery-induced inflammation modified the response to rehabilitation ± PST. Only surgery-induced IL-10 was associated with $\Delta 6MWT_{26\ weeks\text{-}baseline}$ ($P = 0.001$), also adjusted for $6MWT_{baseline}$, age, sex and body mass index (BMI).

Conclusion: In this secondary analysis, only increased surgery-induced IL-10 response was associated with decreased long-term functional performance after TKA. The importance of controlling the surgery-induced immune response remains to be investigated further.

Trial Identification: NCT01351831.

Introduction

More than 10% of individuals older than 60 years have symptomatic osteoarthritis (OA) in the US. The prevalence is likely to rise due to the increasing age of the worlds' population along with the obesity epidemic[1]. Total knee arthroplasty (TKA) can decrease pain

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and disability in patients with end-stage knee OA. However, pain and reduced function may persist despite successful surgery[2,3]. It is not known what causes long-term functional deficits, but inflammation, frailty and arthrogenic inhibition of the quadriceps muscle may be involved[4–7].

Inflammation is part of OA pathophysiology, and the inflammatory state of patients with OA is a marker of OA disease degree, but also reflects non-OA-pathophysiology such as frailty. The inflammatory state of patients undergoing TKA may therefore be a predictor of post-operative recovery[8–11]. However, most studies of trauma and hip or knee surgery found the surgery-induced immune response to be associated with post-operative recovery, infections, and mortality[4,14–19]. Surgery induces a marked immune response, and originally, the immune response to trauma was described as pro-inflammatory followed by an anti-inflammatory response. However, recent studies show simultaneous upregulation of pro-and anti-inflammatory responses, with 80% of the leukocyte transcriptome being affected by trauma[4,14,20,21]. An elevated and/or protracted surgery-induced immune response could originate from post-operative infections. However, the surgery-induced immune response could also predict post-operative recovery by reflecting extent of tissue damage or immunosenescence, thereby reflecting the patient's physiological reserve[4,17–19,22].

We recently conducted a randomized controlled trial (RCT), and found that 7 weeks of supervised physical rehabilitation with progressive strength training (PST) was not superior to supervised physical rehabilitation without PST in enhancing functional performance, knee-extension strength, or knee pain 8 weeks after TKA[2]. In this secondary analysis of the RCT, we wanted to investigate the role of inflammation in long-term recovery of functional performance assessed by the 6-min walk test (6MWT), since most studies have focused on short term recovery and patient reported outcomes. Moreover, we wanted to explore the relation between PST and inflammation, to further assess the tolerability and effect of PST. We investigated the chemokine interferon γ-inducible protein 10 (IP-10) to examine lymphocyte trafficking, and soluble urokinase plasminogen activator receptor (suPAR) as an ageing-related less acutely affected marker[23,24]. Little is known about IP-10 or suPAR in OA or surgery. Moreover, we assessed interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF)-α with a well-established acute response to surgery. IL-6 has both pro-and anti-inflammatory properties and is produced by various cell types including muscle and immune cells[17,25]. IL-10 is an anti-inflammatory marker, and tumor necrosis factor (TNF)-α is a pro-inflammatory marker. Moreover, suPAR, IL-6, IL-10, and TNF-α were chosen as they are associated with low muscle mass, function and poor outcome[23–30].

Our aims were to investigate whether (1) inflammation is associated with 6MWT, knee-extension strength, Knee Injury and Osteoarthritis Outcome Score subscale for activity of daily living (KOOS ADL) and knee pain before TKA; (2) PST affects inflammation after TKA, and how the inflammatory response develop over 6 months; (3) baseline or surgery-induced inflammation modifies the effect of physical rehabilitation ± PST on change in 6MWT (Δ6MWT) following TKA; and (4) baseline or surgery-induced inflammation is associated with Δ6MWT following TKA.

Methods

This is a secondary analysis of data collected in the recently conducted RCT[2]. As stated in the primary trial report (NCT01351831), blood samples were collected and stored in a biobank for future analysis, and this paper reports on analyses of these blood samples as described below.

Ethics

The RCT was approved by the Ethics Committees for Biomedical Research for the Capital Region of Denmark (H-3-2010-106), the Danish Data Protection Agency (2010-41-5357), and was carried out according to the declaration of Helsinki. Oral and written informed consent was obtained from all patients. The RCT was registered at ClinicalTrials.gov (NCT01351831).

Study design and patients

The RCT was designed to assess the effect of 7 weeks of supervised physical rehabilitation ± PST, commenced early after TKA to enhance post-operative function[2], described in brief here. Individuals were randomized 2:2 with a block size of 4 to the PST group and the control (CON) group. Inclusion criteria: age 18–80 years; understanding and speaking Danish; residing near Hvidovre Hospital. Seventy-two patients were included in the primary trial report's per-protocol analysis. All patients followed a standardized, optimized fast-track program for TKA with well-defined discharge criteria with discharge to own home after a median of 2 days[31]. The TKA was performed using a medial parapatellar approach with insertion of tricompartmental prostheses, and tourniquet was applied for all patients as described in Ref. 32. 6MWT, knee-extension strength, KOOS ADL and knee pain were assessed at baseline (secondary analysis: average 9.1 days before TKA; minimum: 1 day; maximum: 34 days) and at 4, 8, and 26 weeks after TKA at the Department of Physical Therapy, Copenhagen University Hospital, Hvidovre, Denmark. Supervised physical rehabilitation interventions took place at 3 outpatient rehabilitation sites in Copenhagen, Hvidovre, and Brøndby counties.

Measures of functional performance, strength, and pain

The RCT was designed to investigate between-group differences in change in the primary outcome: 6MWT from baseline to 8 weeks ($\Delta 6MWT_{8\ weeks\text{-}baseline}$) after TKA[2]. Here, we also chose Δ6MWT as primary outcome, because this performance-based measure of functional performance was shown to be reliable and responsive, and important for patients[12,33,34]. Moreover, we assessed the secondary outcome measures: knee-extension strength, knee pain during 6MWT, and KOOS ADL. The longest distance walked in 2 walk tests was used as the 6MWT. Isometric knee-extension strength was assessed using a strength chair (Metitur Ltd)[35]. Knee pain during 6MWT was assessed using a 0–100-mm visual analog scale (VAS) with end points 0 (no pain) to 100 (worst pain imaginable). KOOS ADL scores ranges from 0 (worst) to 100 (best)[36].

Blood sample measurements

Blood samples with EDTA as anti-coagulant were taken at baseline, immediately before TKA; day 1, week 4, 8, and 26 after TKA, but some blood samples were missing due to logistic difficulties, see Fig. 1. Plasma was separated by centrifugation, aliquoted and stored at −80°C until analyses. IL-6, IL-10, and TNF-α were measured in a high sensitive luminex kit (HSCYTMAG-60SK, Millipore, Billerica, MA, USA). IP-10 and suPAR were measured in samples thawed once with an in house ELISA described in Ref. 37, and the suPARnostic® ELISA (ViroGates A/S, Birkerød, Denmark), respectively. One freeze–thaw cycle does not affect IP-10 or suPAR levels[37,38]. All samples were measured in duplicates following the manufactures instructions. Surgery-induced inflammation was defined as day 1 for IL-6, IL-10, IP-10, and TNF-α; and week 4 for suPAR.