Diplomarbeit

Smoking as a risk factor of total knee arthroplasty

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Declaration

I hereby declare that this diploma thesis is my own original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this diploma thesis. Due acknowledgment has been made in the text to all other materials used.

Graz, May 7, 2021 *Moritz Michael Starzer eh.*

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Glossary and Abbreviations

AAA	Abdominal Aortic Aneurysm
ACL	Anterior Cruciate Ligament
AL	Anterolateral bundle of Posterior Cruciate Ligament
AM	Anteromedial bundle of Anterior Cruciate Ligament
BMI	Body Mass Index
CCK	Constrained Condylar Knee
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
CVD	Cardiovascular Disease
DALY	Disability-Adjusted Life Years
EULAR	European League Against Rheumatism
FB	Fixed Bearing
FEV_1	Forced Expiratory Volume in 1 second
KSS	Knee Society Score
LCL	Fibular Collateral Ligament
MB	Mobile Bearing
MCL	Medial Collateral Ligament
MI	Myocardial Infarction
MPFL	Medial Patellofemoral Ligament
MRI	Magnetic Resonance Imaging
NSAID	Non-steroidal Anti-inflammatory Drug
OA	Osteoarthritis
OECD	Organisation for Economic Cooperation and Development
OR	Odds Ratio
PAD	Peripheral Arterial Disease
PCL	Posterior Cruciate Ligament
PE	Polyethylene
PJI	Periprosthetic Joint Infection
PL	Posterolateral bundle of Anterior Cruciate Ligament
PM	Posteromedial bundle of Posterior Cruciate Ligament
PMMA	Polymethyl Methacrylate
POL	Posterior Oblique Ligament
PROM	Patient Reported Outcome Measure
SDI	Sustainable Development Index
SF-12MCS	Short-form 12 Mental Component Summary
SF-12PCS	Short-Form 12 Physical Component Summary
SHS	Second-Hand Smoke
THA	Total Hip Arthroplasty
TKA	Total Knee Arthroplasty
UKA	Unicompartimental Knee Arthroplasty
US	Ultrasonography
VAS	Visual Analogue Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

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Zusammenfassung

Hintergrund: Das Rauchen von Zigaretten wurde mit postoperativen Komplikationen und einem erhöhten Risiko einer frühzeitigen Revisionsoperation nach primärer Knieendoprothetik (KTEP) assoziiert. Ziel dieser Arbeit ist es, die Komplikationsraten nach KTEPs zwischen RaucherInnen, ehemaligen RaucherInnen und NichtraucherInnen zu vergleichen, um einen Überblick über die diesbezüglichen Verhältnisse in Österreich zu erhalten.

Methoden: Insgesamt wurden 681 PatientInnen, die zwischen 2003 und 2006 an der Abteilung für Orthopädie und Orthopädische Chirurgie am LKH Radkersburg eine KTEP erhalten hatten, retrospektiv nach ihrem Raucherstatus unterschieden. Komplikationen und Revisionen waren während des potentiellen Follow-up von bis zu 17 Jahren dokumentiert worden. Mittels Chi-Quadrat Test wurden Raucherstatus und Revisionen verglichen. Das postoperative Outcome wurde mittels klinischer Scores erfasst: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Visual Analogue Scale (VAS), Short-Form 12 Physical Component- und Mental Component Summary (SF-12PCS/MCS), und dem Knee Society Score (KSS).

Ergebnisse: RaucherInnen, ehemalige RaucherInnen und NichtraucherInnen zeigten keine statisch signifikanten Unterschiede hinsichtlich der gesamten Anzahl an Komplikationen. RaucherInnen (13/46, 28.3%) hatten tendenziell ein höheres Risiko einer Revisionsoperation als NichtraucherInnen (103/596, 17.3%, p=0.062) ohne statistisch signifikanten Unterschied. RaucherInnen (9/46, 19.6%) zeigten ein statistisch signifikant und klinisch relevant höheres Risiko Weichteilkomplikationen zu erleiden als NichtraucherInnen (56/596, 9.4%, p=0.028). RaucherInnen hatten außerdem bessere Ergebnisse im KSS function (79.4 ±24.2, 64.1 ±26.0; p<0.001) und SF-12PCS (41.2 ±10.9, 36.8 ±10.4; p=0.0197) als NichtraucherInnen, gaben präoperativ jedoch stärkere Schmerzen an (8.3 ±1.2, 7.6 ±1.4; p=0.0031).

Schlussfolgerung: RaucherInnen zeigen ein höheres Revisionsrisiko als NichtraucherInnen in Bezug auf Weichteilkomplikationen. Ehemalige RaucherInnen und NichtraucherInnen hatten ähnliche Komplikationsraten, was besonderen Fokus auf die Raucherentwöhnung richtet. Bezüglich des funktionellen Outcomes schnitten alle Rauchergruppen gut ab, was einen positiven Effekt der KTEP unabhängig vom Raucherstatus zeigt.

Abstract

Background: Tobacco smoking has been associated with postoperative complications and an increased risk of earlier time to revision surgery after primary total knee arthroplasty (TKA). In Austria, no scientific evaluation of the outcome of tobacco smoking on TKA has been conducted, despite Austria being a country with a high prevalence of active smokers and a high incidence of TKAs. The aim of this study was to compare complication rates after primary TKA of smoking status groups (active smokers, former smokers, never smokers) in order to provide information about the influence of tobacco smoking on the outcome of TKA in Austria.

Methods: A total of 681 patients who underwent primary TKA between 2003 and 2006 at the Department of Orthopedics and Orthopedic Surgery at the LKH Radkersburg, Austria, were retrospectively evaluated according to the patient smoking status. Complications and revisions were documented during the potential follow-up time of up to 17 years. Smoking status was then analyzed for associations with revision TKA using a Chi-square test. Postoperative functional outcome was measured using clinical scores: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Visual Analogue Scale (VAS), Short-Form 12 Physical Component- and Mental Component Summary (SF-12PCS/MCS), Knee Society Score (KSS).

Results: For the total amount of revisions, no statistically significant difference between active smokers, former smokers, and never smokers could be found. However, a tendency towards active smokers (13/46, 28.3%) having a higher risk of revision surgery than never smokers (103/596, 17.3%, p=0.062) was present without a statistical preference. Subgroup analysis revealed a higher risk of soft tissue complications for active smokers (9/46, 19.6%) in comparison to never smokers (56/596, 9.4%, p=0.028). Smokers scored higher at KSS function (p<0.001) and SF-12PCS (p=0.0197) than never smokers and reported higher pain ratings preoperatively (p=0.0031).

Conclusion: Smoking causes an increased risk of revision surgery in case of active smokers compared to never smokers. Former smokers and never smokers had similar complication rates, indicating a benefit of smoking cessation on outcome after TKA. Our study shows a benefit in functional outcome after primary TKA regardless of smoking status.

1 Introduction

Osteoarthritis (OA) is a significant cause of disability globally, with knee osteoarthritis having the highest prevalence among all age groups (1, 2). It is a multifactorial disease that ultimately destroys the synovial joint, leading to pain and functional loss (3). Treatment options for knee OA are mostly symptomatic and range from conservative measurements to total knee replacement – or arthroplasty (TKA) – being the most extensive procedure if the disease's severity dictates the necessity (4). As age and obesity demonstrate two major risk factors for developing OA, the joint disease will be of high clinical and socioeconomic significance in an increasingly older and more obese population (5-7).

Complimentary to the high prevalence of knee OA, TKA is one of the most commonly performed and cost-effective elective surgeries, with Austria being one of the highest-ranked regarding numbers of knee replacement surgeries performed among all OECD countries (7, 8). Improvement of quality of life by reducing pain and regaining function is the leading patient-based indication for surgery. An overall good outcome of TKA affirms this with pain relief and better mobility being the most mentioned improvements by patients following surgery (9). Nevertheless, there is a risk of residual functional limitation and pain or other complications, possibly leading to revision surgery, all of which potentially decrease the outcome and patient satisfaction (10, 11). The outcome of knee replacement surgery can be measured in several ways, including morbidity and mortality rates after surgery, functional outcome, patient defined satisfaction, and implant failure rates (12, 13). Therefore, it is of utmost importance to identify and minimize possible causes and risk factors leading to residual defects, functional limitation, and revision surgeries.

Smoking has been described as a leading general health risk by numerous studies throughout the last 40 years and is ranked first for all-cause all-age deaths among men and ranked eight among women (14). Smoking rates of 24% in Austria surpass the OECD average of 18% with slightly rising numbers in recent years, bringing special attention to smoking as a risk factor for the Austrian population regarding health in general and knee replacement surgery especially (7). Smoking has been identified as a considerable risk factor for decreasing outcomes following TKA. Previous studies have shown a correlation between smoking and postoperative complications and an earlier time to revision surgery (15, 16). These results further

solidify the assumption that there is a particular need to find more evidence on the impact of smoking on orthopaedic surgeries, especially in Austria, as a country of high prevalence.

2 Gross & Functional Anatomy of the Knee Joint

As the lower limb's intermediate joint, the knee joint allows movement between the femur, tibia, and patella and therefore is a compound joint consisting of the femorotibial and the patellofemoral joint (17). Knowledge of knee joint anatomy and biomechanics is essential for understanding physiological processes and, therefore, diagnosing and treating acute or chronic injuries involving the knee. This is especially true for knee replacement surgery, where the underlying processes, e.g., rheumatoid arthritis or aberrant leg axes (varus or valgus knee) would require different surgical approaches.

Analogous to general joint anatomy, the knee joint consists of osseous structures and the corresponding articulate surfaces, the surrounding articulate capsule, synovia, menisci, numerous ligaments, bursae, and synovial tendon sheaths. Movement is ensured by muscular insertion around the joint. As a whole, this joint system should distribute impacting forces evenly and provide movement of the corresponding osseous structures (18). The following chapters will describe the most important anatomical structures in more detail.

2.1 Osseous Anatomy

The knee joint (lat. articulatio genus) is the biggest joint in the human body and consists of the femur, tibia, and patella. As not all bones directly articulate with each other, the knee joint can be subdivided into two joints, patellofemoral (formed by patella and femur) and femorotibial joint (formed by femur and tibia). Tibia and fibula form a separate joint (tibiofibular joint) with anatomical proximity to the knee joint. It may show a connection to the knee joint, but does not participate in its formation (18, 19).

The femur is the longest bone in the human body and can be divided into corpus, collum and, caput. Hyaline cartilage covers the caput, which is part of the hip joint (lat. articulatio coxae). The distal portion consists of two condyles connected by the patellar groove ventrally, a glide surface for the patella, and divided by the intercondylar fossa dorsally (20). The condyles show a larger convex curvature dorsally than ventrally and a slighter curvature laterally than medially (18). This means that the curvature radius becomes continually smaller and that the curvature centers are positioned on a spiral. This accounts for no transversal axis but rather

multiple axes and therefore allows distinct movements within the knee joint. The lateral condyle is wider ventrally than dorsally, whereas the medial condyle shows an even width. An even, horizontal contact face while standing upright is provided by a tilt of the femoral axis (19).

The tibia consists of the large trigonal shaft, an upper part, and a lower part forming malleoli together with the fibula and articulating with the talar bone. The upper part ends in the medial and lateral condyles covered by hyaline cartilage and forming the surface area to which the femoral condyles articulate. In between lies the intercondyloid eminence that divides the area into an anterior and posterior intercondyloid area to which the posterior cruciate ligament (PCL), the anterior cruciate ligament (ACL), and both menisci are attached. The anterior surface beneath the condyles is called the tibia's tuberosity to which the patellar ligament is attached (18, 19). The medial tibial plateau's articular surface is concave, whereas the lateral plateau has an anteroposterior convexity (17). The incongruency between the tibial surface area and the femoral biconvex condyles is compensated by both menisci (18).

The patella, the largest sesamoid bone in the body, is a triangular-shaped bone with the base being proximal and the apex being distal. It has an anterior surface and an articular surface (femoral side), which is located on the proximal two-thirds of the patella's underlying surface and is divided into a medial, a broader lateral, and a smaller more medial odd facet (17, 20). The anterior face is embedded in the quadriceps tendon, and the patella tendon is attached to its apex (19). The patella serves as a pulley by increasing torque and improving quadriceps strength (20, 21).

2.2 Ligaments

Ligaments are the fibrous connective tissue – mainly collagen – that form connections between bones and provide stability within joints. A complex arrangement of intra- and extracapsular ligaments further enhances stability in the knee joint but also strengthens the articular capsule, provides for proper guidance for the gliding surfaces, and inhibits unphysiological movement (18, 21).

2.2.1 Anterior and Posterior Ligaments

The most prominent anterior structure is the patellar ligament running from fibrous connections of the quadriceps muscle to the tibial tuberosity, where it forms the connection between the patellar apex and tibia (18). The retinacular connections, fibrous continuations of the vastus medialis and lateralis, run alongside the patella and have distal attachments at the tibial condyles. They form the anterior part of the articulate capsule (18, 21). Between the adductor tubercle above the medial femoral epicondyle and medial patella lies the medial patellofemoral ligament (MPFL), providing resistance against the patella's lateral movement. It is rather part of the transverse retinacular structures than it is a sole ligament itself but is an essential stabilizer of the knee (17, 19, 22).

The posterior part consists of posterior fibers and the oblique popliteal ligament. The posterior fibers form the posterior part of the articulate capsule. The oblique popliteal ligament is part of the semimembranosus muscle's distal attachment, which inserts at the profound pes anserinus on the tibia. The ligament attaches to the lateral femoral condyle and serves as a posterior reinforcement for the articulate capsule (18, 21)

2.2.2 Medial and Lateral Ligaments

The medial knee's primary stabilizers are the tibial collateral ligament (medial collateral ligament, MCL) and the posterior oblique ligament (POL). The MCL stretches from the medial femoral epicondyle to the medial tibial condyle and can be divided into an anterior and a posterior part as well as into a superficial and deep layer (22). The anterior part has no connection to the medial meniscus and, therefore, no connection to the articulate capsule. The posterior part is fused to the meniscus but relaxes during flexion and therefore provides for rotational ability when the knee is flexed (17, 18). The POL stretches from the adductor tubercle to the posteromedial part of the medial tibial condyle where it reinforces the articulate capsule and is a restraint to internal rotation and valgus translation (21, 22).

The lateral knee is stabilized by the fibular collateral ligament (LCL), the popliteofibular ligament, the arcuate popliteal ligament and the anterolateral ligament. The LCL stretches directly from the lateral femoral epicondyle to the fibular head where it has no connection to the lateral meniscus and therefore runs

extracapsular. It resists varus stress in extended knee position (18). The popliteofibular ligament attaches to the popliteal tendon and the fibular head and resists external rotation. The arcuate popliteal ligament stretches from the lateral femoral condyle to the posterior fibular head and reinforces the fibrous articulate capsule (18, 21). The anterolateral ligament originates at the lateral femoral epicondyle and inserts at the lateral tibial condyle. It provides for resistance against internal rotation (23).

2.2.3 Central Ligaments/Cruciate Ligaments

The cruciate ligaments are the central ligamentous structures in the knee joint between the joint capsule's synovial and fibrous layer, therefore lying intracapsular but extraarticular (18). With origins at the intercondylar notch and insertion points near the intercondylar eminence, they are crucial for anteroposterior stability but also provide for surface adhesion during flexion in the knee joint (19, 21).

The anterior cruciate ligament (ACL) consists of two bundles, the posterolateral (PL) and the anteromedial (AM) bundle. The ACL originates from the posteromedial side of the lateral femoral condyle and inserts in the anterior intercondylar area on the tibia (24). The PL bundle is tight at full extension, whereas the AM bundle is tight at flexion (tightest at 60% and 90% flexion, respectively) (21, 24). The ACL resists anterior translation of the tibia against the femur and internal rotation (18).

The posterior cruciate ligament (PCL) as well consists of two bundles, the anterolateral (AL) and the posteromedial (PM) bundle. It originates from the anterolateral side of the medial femoral condyle and inserts in the posterior intercondylar area (25). The AL bundle is tight in flexion; the PM bundle is tight in extension, whereas the PCL's most significant stabilizing contribution is in flexion to resist posterior translation of the tibia against the femur (18, 21).

2.3 Cartilage and Menisci

The joint surfaces are covered by a layer of specialized articular cartilage, which, combined with the underlying calcified cartilage and bone, form a distinctive functional composite to transfer loads during weight-bearing and joint motion (26). The cartilage matrix is populated by a single cell type, the chondrocyte, and consists of water (more than 70%) and organic extracellular components. Those are mainly type II collagen and aggrecan or other proteoglycans plus other collagens and non-

collagenous proteins (27). The collagen network provides tensile strength, and proteoglycans provide resilience during compression. Like a sponge, proteoglycans accumulate water when the cartilage is decompressed due to their water storage capacity, while the collagen network prevents the proteoglycans from expanding too much. During compression, the proteoglycans release the stored water to allow for the articular cartilage's weight distributing abilities (28, 29).

Due to the articular surfaces' incongruency, the knee has two weight-bearing and -distributing C-shaped structures composed of fibrocartilage (18, 30). Both are triangular-shaped in cross-section and are located between femur and tibia. The meniscal tissue is differently vascularized from inside to outside and can therefore be classified into three zones: red-red (RR), red-white (RW), and white-white (WW). RR is at the base of the meniscus at the synovial membrane and shows the best vascularization, RW shows intermediate vascularization, and WW is avascular and needs passive diffusion for extraction of nutrients from the synovia (21, 30). Latest research suggests avoiding this classification as vascularization changes throughout life and is often not directly assessable during surgical procedures (31). The medial meniscus is broader and thinner than the lateral meniscus, and its horns are further located from each other which provides stability. The posterior part of the MCL connects to the medial meniscus (17). The lateral meniscus is rounder than the medial meniscus and can move better. It has no connection to the LCL, which further provides more mobility (17, 18).

2.4 Muscular Anatomy

The knee joint is surrounded by musculature, allowing for joint motion and enhancing the ligaments' stabilizing function.

2.4.1 Extensors

The essential extensor muscle at the anterior thigh is the quadriceps muscle. It consists of vastus lateralis, medialis, and intermedius and the rectus femoris muscle. The vastus muscles originate from the femoral shaft (the rectus femoris originates from the anterior inferior iliac spine), merge into a single tendon (quadriceps tendon), and insert at the base of the patella. As an extension from its apex, it continuous to the tibial tuberosity as the patellar tendon (17, 18). A decrease in quadriceps strength is associated with the onset of osteoarthritis of the knee (32).

Another extensor is the sartorius muscle, which originates from the anterior superior iliac spine and inserts in the pes anserinus and also assists in internal rotation (18).

2.4.2 Flexors

The flexor muscles are the biceps femoris muscle, the semitendinosus muscle, the semimembranosus muscle, and the gracilis muscle. The biceps femoris consists of two heads, which originate from the ischial tuberosity (long head) and posterior femoral shaft (short head) and insert in the fibular head (18). It also assists in external rotation. The semitendinosus and semimembranosus originate from the ischial tuberosity and insert in the superficial pes anserinus (semitendinosus) and the profound pes anserinus (semimembranosus), where they assist in internal rotation. The gracilis originates from the inferior part of the pubic bone and inserts in the superficial pes anserinus (22). Additional flexors are the gastrocnemius muscle and the popliteus muscle (18).

2.5 Biomechanics

The orthopedic guiding principle *form follows function* underlines the necessity of understanding the biomechanical aspects during knee stance and motion. Knee surgery, and especially TKA, aims to restore the lower limb's functional capacities by restoring the anatomical structures to as close as possible to ensure proper function (33). Therefore, a biomechanical understanding is crucial for successful knee surgery.

2.5.1 Axes

Two axes (anatomical and mechanical) can be allocated to assess the individual lower limb's biomechanical properties. These axes not only are a predictor for the onset of OA when misaligned but are essential aspects of pre- and postoperative planning and management of TKAs as well (34, 35). The anatomical axes of femur and tibia are lines drawn through their respective intramedullary canals. An ideal position would be for the femoral axis to sit in 9° of valgus in relation to the midline and the tibial axis to sit 3° of varus relative to the midline (36). This constellation accounts for an externally oriented angle between femur and tibia of 172-177° (physiological valgus knee angle) (37).

The mechanical axis is a line drawn through the femoral head and the ankle. It consists of the femoral and tibial mechanical axes. The anatomical and mechanical tibial axes are nearly identical, whereas the mechanical and anatomical femoral axes form an angle of 5-7° (38). However, in recent years, the concept of a constitutional varus has arised and therefore, only 30% of people might have a physiological long leg axis as described (39).
With a description of those axes arise the problem of malalignments in the knee joint (37):

- Genu varum: increased angle between femur and tibia; mechanical axis moves medially
- Genu valgum: decreased angle between femur and tibia; mechanical axis moves laterally
- Genu recurvatum: mechanical axis moves anteriorly

2.5.2 Range of motion

The knee joint offers six degrees of freedom, whereas the main principle of knee joint kinematics is rolling, gliding, and rotation. Rotational movement is possible through extension/flexion, internal/external rotation and varus/valgus. Translational movement is anterior/posterior, medial/lateral, and compression and distraction (40).
Active extension is possible up to 0° and -10° passively according to the neutral zero method. While extending the leg, the cruciate ligaments get tensioned before full extension is achieved. Therefore, the tibia rotates externally at the free leg (or the femur rotates internally at the standing leg), the ACL relaxes, and further extension is possible. Additionally, the collateral ligaments get tensioned and prohibit internal and external rotational movement in extension. In flexion internal (up to 10°) and external (up to 40°) rotation are possible. Active flexion is possible up to 120°, and passive flexion is possible for up to 160° before soft-tissue impingement (18).

3 Osteoarthritis of the Knee Joint

3.1 Definition

Osteoarthritis (OA) does not only affect the knee joint but is a degenerative joint disease of small (such as those in the hand) and large (such as the knee and hip joints) diarthrodial joints. Tear-and-wear of the cartilage was the defining mechanism of OA for a long time. However, recent studies confirm that it rather is a whole joint disease that not only involves structural changes in the articular cartilage but also in subchondral bone, ligaments, capsule, synovial membrane and periarticular muscles (41). Structural changes include loss of cartilage, osteophyte formation, subchondral bone changes, and meniscal alterations, which can be seen using radiography and MRI and which may be accompanied by pain (42, 43).

Prevalence data for OA of any location varies widely depending on the definition and classification criteria used, but research suggests a higher prevalence for radiographic OA than for symptomatic OA and for knee and hand OA than for hip OA (44). OA of any location globally in 2010 was the 11th highest cause of years lived with disability, affecting over 250 million people or 4% of the world's population (45).

Knee OA is the most common location of OA, with a global prevalence estimated to be 3,8% with peaks at the age of 50 (1). It affects the whole knee joint and shows typical clinical and radiographic signs of OA leading to pain and ultimately breaking down of the whole knee joint structure and function (46). In combination, this leads to knee OA accounting for approximately 85% of OA burden worldwide (2).

Depending on the affected compartment of the knee, the disease can be subdivided into the following locations:

- Unicompartmental patellofemoral OA
- Unicompartmental femorotibial OA
- Bicompartmental femorotibial OA
- Tricompartmental patellofemorotibial OA (pangonarthritis)

Moreover, OA can be classified by the medial or lateral part of the knee affected, thus dividing into varus- and valgus-OA.

3.2 Etiology

OA can be classified as primary (or idiopathic) and secondary. Idiopathic OA is characterized by an onset without any preceding diseases or injuries that could have been causative. Secondary OA develops secondary to recognized and precisely defined causative factors (26). Differentiation into primary and secondary OA applies to OA for any location. Therefore, it is also valid for OA of the knee.

Primary Osteoarthritis
– Localized – Generalized   – Three or more joints affected – No causative condition – Probably multifactorial
Secondary Osteoarthritis

– Mechanical extraarticular factors
  – Axial Malalignment
  – Instabilities of ligaments
  – Muscular Dysbalances
  – Microtrauma
– Mechanical intraarticular factors
  – Meniscal lesions
  – Meniscectomy
  – Posttraumatic
– Inflammatory Diseases
  – Rheumatoid arthritis
  – Bacterial arthritis
– Metabolic factors
– Connective tissue disease
  – Marfan syndrome
  – Ehlers-Danlos-syndrome
– Drug-induced
  – Chemotherapy

Table 1. Primary and Secondary Osteoarthritis (38, 47).

3.2.1 Risk factors

Risk factors for OA can be divided into person-level factors that increase the level of individual susceptibility and joint-level factors (i.e., factors that alter the biomechanical stability) (48).

3.2.1.1 Person-level risk factors

Age is one of the most prevalent risk factors of OA. The hypothesis is that a multifactorial mechanism leads to joint damage and loss of function. Processes included are oxidative damage, thinning of cartilage, muscle weakening, and a

reduction in proprioception (48). With age goes sarcopenia, which for itself has been described as a risk factor of knee OA, especially for quadriceps weakness (32).
Obesity, defined as a body mass index > 30kg/$m^{2,}$ is strongly associated with knee OA, whereas overweight (BMI > 25kg/m^2 to BMI < 30kg/m^2) has a lower risk but is also a significant risk factor (5). Research describes weight loss to positively influence pain, function, and low-grade-inflammation (49). The association between OA and metabolic syndrome suggests that obesity may be a risk factor due to increased joint loading and systemic factors (50).
Female gender is at higher risk of developing knee OA, potentially due to hormonal factors, and other parameters such as reduced volume of cartilage, bone loss, or muscle weakness (5, 51).

3.2.1.2 Joint-level risk factors

Previous knee injury increases the risk for the onset of OA (5). ACL rupture leads to early-onset knee OA in 13% after 10 to 15 years. When associated with damaged cartilage, subchondral bone, or menisci, the prevalence is higher between 21% and 40% (48).
Abnormal loading of joints or repetitive high joint usage is associated with the onset of knee OA. Especially occupational activities that involve repetitive squatting and kneeling show an increased risk of developing knee OA (52). Moreover, several high impact sports have been reported as moderate to strong risk factors of knee OA, which might be associated with an increased risk of injury (53).
Malalignment is rather a predictor for progression of knee osteoarthritis than a risk factor of onset. Increased structural degradation is caused in the compartment under the highest stress: medial progression of knee osteoarthritis four-fold greater with varus alignment and lateral progression five-fold greater with valgus alignment (48).

3.2.2 Pathogenesis

Contrary to the standard description of osteoarthritis being a passive degenerative disease, it rather is an active dynamic alteration arising from an imbalance between repair and destruction of joint tissues (54, 55).

In osteoarthritis, the cartilage matrix changes composition and structure and loses its integrity. As a consequence, the cartilage shows increased susceptibility to disruption by physical forces. Initially, erosions at the surfaces are noticeable, which later progress to deep fissures in the cartilage accompanied by enlargement of the calcified cartilage zone (26, 54). The chondrocytes show increased synthetic activity in an attempt to repair the damaged surfaces (26). During this process, they also generate pro-inflammatory mediators that impair chondrocyte function and stimulate synovial inflammation and proliferation, accompanied by a pro-inflammatory response, hypertrophy, and increased vascularity (54).

The subchondral bone shows increased bone turnover, and vascular invasion of the cartilage (54). The subchondral plate is thickened, especially in areas where severe cartilage damage and bone marrow lesions are apparent but may also occur in areas without obvious damage (26, 54). These changes in subchondral bone may not only occur in later stages of osteoarthritis but eventually initiate cartilage damage (26, 56).

During these processes, patients experience pain as a highly disabling symptom of osteoarthritis. Patients may feel pain differently, wherefore, apart from peripheral nociceptive pain mechanisms, neuropathic pain mechanisms and central pain mechanisms have been hypothesized and identified to be responsible for the pain experience (54). Nociceptive pain is due to the altered structures (apart from cartilage, which is avascular and aneural) and the accompanying inflammation. The inflammation causes a peripheral sensitization of joint nociceptors, which respond more intensely to noxious and non-noxious stimuli (55). Central sensitization results in pain hypersensitivity by increasing spontaneous neuronal activity, reducing activation thresholds and expanding the receptive field. It involves excess nociceptive ascending and deficient inhibitory descending signals. (55) Neuropathic pain arises from nerve damage in the joint, the peripheral nervous system, or the spinal cord (55). Both central sensitization and neuropathic pain could explain the interindividual difference between patients regarding pain perception. Imaging abnormalities of osteoarthritis are often seen but do not necessarily correlate with the experienced pain (57). Therefore, other mechanisms could be the driving factor for pain perception, and the ones mentioned above are hypothesized to be relevant (55).

3.3 Diagnosis

3.3.1 Clinical Symptoms

The biggest contributing symptom to disability regarding knee OA and a driving factor for consultation of health professionals is pain occurring during weight bearing. Due to varying innervation of the knee joint and inter-individual differences in pain perception, the onset of pain between patient groups may be variable and often incongruent to the radiographic alterations and signs (i.e., structural OA), which may take years to appear (58). Pain may start slowly and may only be restricted to distinct movements and weight-bearing in early phases but eventually exacerbates pain in advanced stages when resting and sleeping (56, 59).

Functional limitations in terms of loss of range of motion are often present and may partly be caused by synovial effusion. Short-lived morning stiffness is also included as a criterion for OA (59, 60).

3.3.2 Clinical Diagnosis

Knee OA can be diagnosed by patient history and clinical examination. Precise diagnoses also help differentiate between pain caused by OA and pain caused by another underlying diseases such as pain referred from the hip or the back in case of coxarthrosis or lower back pain (61).

An initial assessment should primarily focus on identifying the influence of OA on function, social participation and relationships, occupation, quality of life, leisure activities and sleep (54). The symptoms mentioned above should be examined, and pain quality should be identified as OA pain is often described as a dull, intermittent ache, localized to one compartment, contrary to acute inflammatory or traumatic pain. Additionally, information on risk factors, relevant comorbidities, occupation, family history of OA, and previous knee injuries should be gathered (54, 59, 61).

Physical examination should include body habitus and gait pattern as well as axial malalignment. Additionally, signs may include crepitus on active or passive motion, restricted movement, ligamentous instability, and bony enlargement (59).

In summary, a clinical diagnosis may be sufficient to make a precise diagnosis without imaging techniques. According to the EULAR recommendations from 2010 (59), a clinical diagnosis may be made according to three symptoms (knee pain,

short-lived morning stiffness, and functional limitation) and determination of three signs on examination (crepitus, restricted movement, and bony enlargement).

3.3.3 Imaging Techniques

Recommendation
1. Imaging is not required for the diagnosis of OA in typical cases.
2. Atypical presentations may require imaging to confirm the diagnosis of OA or make alternative or additional diagnoses.
3. Routine imaging in follow-up is not recommended except for unexpected rapid progression of symptoms.
4. Plain radiography is the gold standard. US and MRI may be used for additional soft tissue diagnoses, CT for bone.
5. Radiographic views are important for optimizing detection of OA.
6. Imaging is not recommended for predicting non-surgical treatment response
7. Imaging may improve accuracy regarding intraarticular injections.

Table 2. Adapted from EULAR 2017 recommendations for imaging techniques for the diagnosis of osteoarthritis (57)

Plain radiography is the gold standard in diagnosing structural alterations of the bone (57). Other imaging modalities include MRI, ultrasonography (US), CT, and nuclear medicine techniques (scintigraphy, positron emission tomography).
EULAR recommendations for the use of imaging techniques regarding osteoarthritis are listed in table 2.
When plain radiography is indicated, it is vital to consider the appropriate radiographic views to fully assess the structural alterations. Views include standing weight-bearing a.p. and lateral views in full extension and flexion for the tibiofemoral joint and skyline and lateral projections for the patellofemoral joint (57).
Concerning the structural alterations and the resulting classification, many grading systems are available to assess severity, but the one used the most is the classification developed by Kellgren and Lawrence, described in table 3. Figure 1 shows plain radiographs using the Kellgren and Lawrence grading system.

Grade 0	No presence of osteoarthritis
Grade 1	Possibly slight narrowing of joint space and osteophyte formation
Grade 2	Narrowing of joint space, osteophyte formation
Grade 3	Definite narrowing of joint space, moderate osteophyte formation, sclerosis, deformity of bony structures
Grade 4	Severe narrowing of joint space with marked sclerosis, large osteophyte formation, and definite deformity of bone ends

Table 3. Kellgren-Lawrence classification system (62)

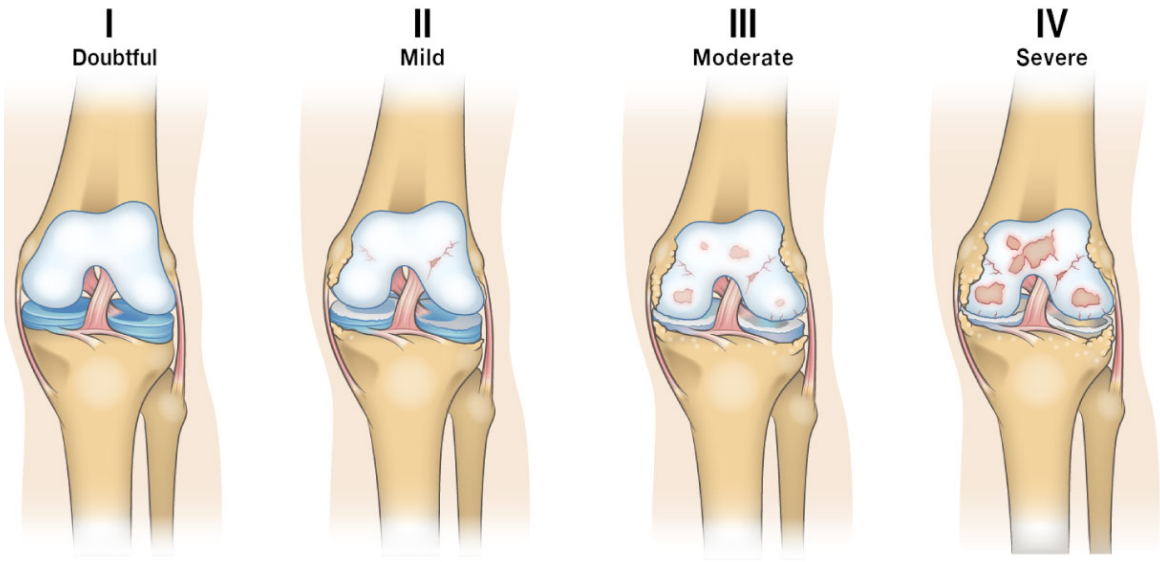

Figure 1. Schematic presentation of knee OA using the KL classification system criteria described in table 3.

Source: https://springloadedtechnology.com/wp-content/uploads/2020/09/Kellgren-Lawrence-Stages-of-Knee-Osteoarthritis.jpg [last access: 28.12.2020, 10:05]

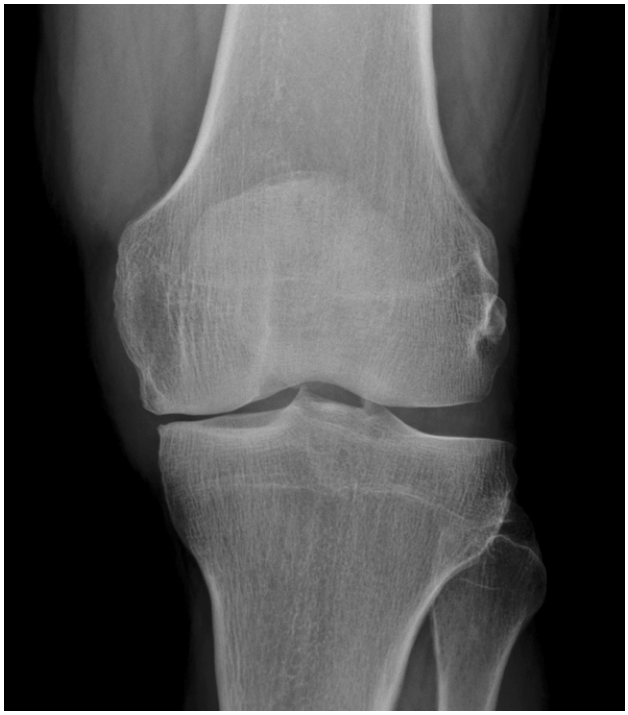

Figure 2. KL Grade 3. There is moderate osteophyte formation and sclerosis but a definite narrowing of the joint space.

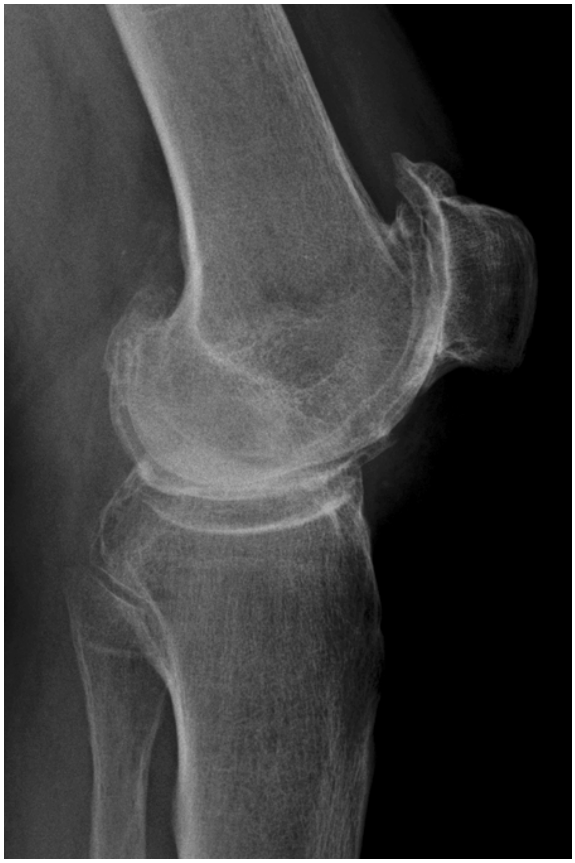

Figure 4. The same knee as in figure 3 with KL grade 4 in lateral view.

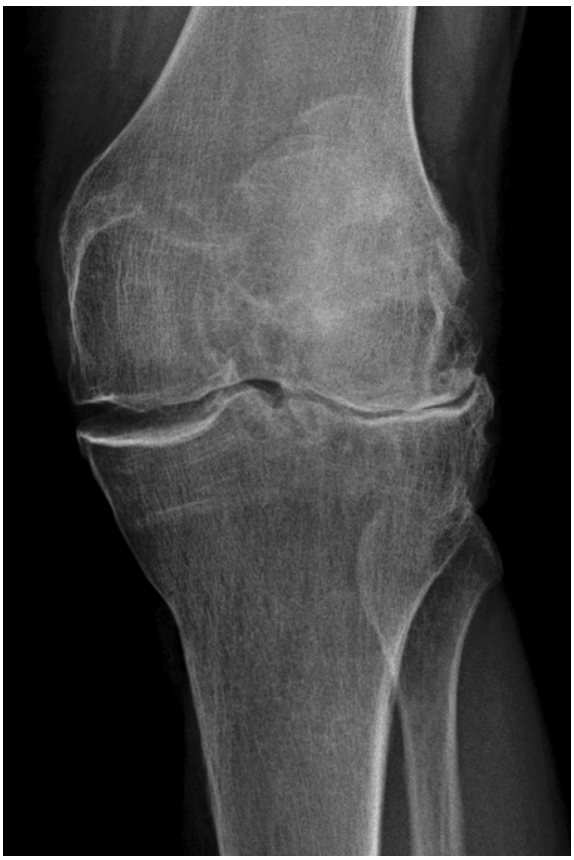

Figure 3 KL Grade 4 in AP view. Severe narrowing of joint space with sclerosis, osteophyte formation and bony deformities.

3.4 Therapy

As mentioned in the guidelines, key treatment strategies are mostly non-pharmacological and should focus on education and self-management, exercise and weight loss, assistive devices, alternative and complementary approaches (63). If severity progresses, surgical intervention can be considered (64).

3.4.1 Conservative Treatment

As part of a multimodal therapeutic approach, education and self-management are strongly recommended to manage osteoarthritis. Information on treatment modalities, the disease itself, the pathophysiology as well as diagnostic imaging may improve patient compliance and enhance the outcome of variable treatment approaches (65).

Exercise therapy is especially helpful in decreasing pain and improving joint motion (66). Land- and water-based low-impact aerobic exercise is considered the exercise regimen with the most substantial positive impact. More precisely, exercise recommendations include motion/flexibility exercises, quadriceps strengthening, or endurance/strengthening exercises (63, 64, 67). Weight loss, as mentioned above, may be helpful in patients with BMI > 25kg/m^2 (49, 68, 69). Moreover, a combination of exercise and dietary weight management seems to provide better effects on pain and function than exercise or diet alone (69).

Assistive devices such as knee braces and heel wedges may be used but are not generally recommended contrary to walking aids such as crutches, canes, and walkers. Elevation of chairs and beds may as well be beneficial in order to improve the overall quality of life (63).

Analgesics most often recommended include paracetamol and topical or oral NSAIDs. Recent literature suggests the use of oral NSAIDs over paracetamol as first-line and single treatment. The administration should aim at short-term use at the smallest dose possible (70). Topical NSAIDs are considered other first-line methods, with lesser systemic side effects but still measurable effects (71). Intra-articular corticosteroids are recommended for patients who do not respond to oral or topical analgesics in short-term and hyaluronic acid for long-term treatment (63). For refractory symptoms, opioids such as tramadol, in particular, are recommended, and duloxetine, a serotonin and norepinephrine reuptake inhibitor, can be

considered (63). However, the better the effect of conservative therapies, the more severe potential side effects have to be expected.

3.4.2 Surgical Treatment

Surgical interventions may be indicated if the disease progresses and pain and functional impairment intensify. The different approaches are discussed controversially in the literature and corresponding guidelines (63).

Knee osteotomy aiming at re-alignment of the joint axis is associated with benefits in pain and function. Its use is restricted to unicompartmental knee OA, as the procedure aims at a load transfer from the affected compartment to the one (54). It is mainly considered for young and active patients and can postpone joint replacement surgery for up to 10 years (72). Older, more inactive patients have a greater benefit from unicompartmental knee endoprostheses due to shorter rehabilitation time and faster recovery period (72).

In general, arthroscopic procedures with cartilage smoothing, removal of loose bodies, and synovectomy are not recommended despite its wide usage in the early management of OA (63). Given the minimal benefits and potential harms, arthroscopy should not be the primary focus in the management of OA (73).

Today, joint replacement surgery is considered a clinically appropriate and cost-effective treatment for late-stage OA (74). It should be restricted to patients with more severely affected functional status after all appropriate conservative options have failed (54, 74).

4 Total Knee Arthroplasty (TKA)

4.1 Epidemiology

Treatment of OA with knee endoprostheses continues to increase in usage globally, as reported by many joint registries worldwide (8). Total numbers of performed knee replacement surgeries are variable due to population differences but have reached 700.000 per year in the USA. Furthermore, prevalence data from 2010 has shown a prevalence maximum of 1,5% in the general population and 10,4% in patients aged 80 years (75). Estimations suggest that the use of TKA will continue to increase in the future (76).

Literature from 2018, analyzing the number of TKAs performed in Austria and its relation to demographic changes from 2009 to 2015, suggests a trend towards increasing numbers of TKA. A 13% increase in TKA has been observed over six years, together with an increase of 1.1% in the population aged 50-90 (77). These changes also accounted for Austria having the highest rate of TKA per inhabitant among OECD countries in 2014 (77). The same development has been demonstrated for 2019 (227/100.000) (7). The average age of patients undergoing TKA in Austria was 69.6 years, similar to other developed countries (8, 77). Likewise, in the patient group aged 60 years and younger increasing numbers of TKA have been observed, which may partly explain the growing number of revision surgeries (76). Recent evidence suggests that this patient group had an increased lifetime risk of revision surgery of 35% for men and 20% for women, with half of revision surgeries occurring within the first five years after primary surgery (78).

The increasing demand for TKA may also be in part explained by demographic changes in terms of an elderly population and increasing numbers of obesity but may not solely be caused by them (79). Ongoing development of medical care, a growing number of knee injuries, and expanding indications for the procedure also seem to be responsible for increased intervention numbers (77, 79).

4.2 Development of TKA

The first surgical trials for the treatment of knee osteoarthritis date back to as far as the mid 19th century when Verneuil described an excision arthroplasty by the interposition of soft tissue to prevent bony ankylosis (80). In 1890 the German surgeon Gluck presented the first knee prosthesis made of ivory. Highly septic

conditions led to infection and early implant failure, which – in combination with complex fixation components – did not provide ideal circumstances for further use (81).

Advancements in hip endoprostheses in the mid 20th century also marked the beginning of a new generation of knee endoprostheses. Though the newly developed techniques showed success, progress in modification of total knee endoprostheses was limited due to complex anatomical and biomechanical differences within the knee in comparison to the hip joint (81).

Sir John Charnley achieved a developmental milestone in 1961 with his *Low Friction Arthroplasty*. The usage of polymethylmethacrylate (PMMA) for implant fixation and the combination of metal and polyethylene laid the foundations for modern endoprosthesis designs (82). Charnley's invention led to the first implantation of an actual surface layer prosthesis by Gunston in 1969 by using a femoral component and tibial inlays (83). Engelbrecht further developed this system as an unicondylar joint replacement (84).

With the introduction of the full bicondylar joint replacement by Walker, Insall, and Ranawat in 1974, the endoprosthetic era underwent another upswing in usage and development (81, 85). During the following years, standardized procedures were introduced and surface materials improved (81).

4.3 Indications and Contraindications

As previously mentioned, knee replacement is considered the ultimate treatment modality if conservative methods and less invasive surgical procedures do not provide enough functional benefit and pain reduction (86).

Traditionally, patients with morbid obesity (higher risk of perioperative complications), as well as patients younger than 55 (increased risk of an earlier time of revision), have more likely been excluded from the decision-making process (8, 78, 87). The same applies to patients suffering from severe medical comorbidities, widespread pain, and catastrophizing behavior, as these factors are associated with a higher risk of persistent pain postoperatively (88, 89).

Recent studies suggest reconsidering classic indications and contraindications. Although morbid obesity is associated with a higher risk of perioperative complications, patients with a BMI of more than 35 or even higher seem to benefit

from knee replacements regarding pain relief as much as normal-weight patients (87, 90).

Although a declining and not-improving functional status may be an indicator of inevitable TKA, studies have shown an association between worse functional status preoperatively and worse functional status postoperatively. This association suggests being cautious in letting the patient's functional status deteriorate to prevent a worse outcome (91).

The shared decision-making model enables the patient to participate in the decision-making process, whether to undertake TKA or try conservative measures. The widely recommended and adopted use of this model empowers the surgeon to reconsider and broaden the indications of TKA (92). This is especially necessary in patients being on either end of the age spectrum, as an earlier time of revision (in patients younger than 55) or higher risk of complications (patients aged 80-90) have to be weighed against functional improvements and improved quality of life. The patient is the ultimate entity to decide for or against surgery, depending on the individual needs (86).

Nevertheless, adequately informed and educated patients are necessary to prevent exaggerated expectations and a disappointing result. This requires the clinician to focus on explaining alternative treatment methods as well as providing realistic results, depending on the patient's pre-existing condition, functional status, and prospective lifestyle (81).

4.4 Materials

In implant-design, the choice of materials is one key-point to produce well-functioning prostheses and minimize the risk of complications. Special attention is directed to wear of the different components to achieve high durability and biomechanical properties in terms of sliding behavior, which in turn as well prevents wear of the components involved. Biologically compatible materials should be used to minimize the risk of complicated allergic and septic reactions that can worsen the outcome of the procedure (93).

Nowadays, conventional implant designs are made of cobalt-chromium-alloys and pure titan or titan-alloys. Knee endoprostheses are mostly produced using a cobalt-chromium-molybdenum-alloy (CoCrMo) (94). As for the inlay, the standard material

is polyethylene, which has been developed by increasing the molecular weight to produce so called ultra-high molecular weight polyethylene. This material, combined with sterilization processes using ionizing radiation, reduces wear, and increases durability significantly (95, 96).
Materials used for anchoring the components to the bone are dependent on the type of anchoring. Three types can be distinguished: cemented, cementless, and a hybrid fixation where both types are combined. The cement used is PMMA, whereas the cementless type fixation requires specific materials used in the implant itself – mainly titanium-alloys or tantalum. Those materials are osteoconductive and provide the requirements for integration into the bone (93).

4.5 Implant Designs

The choice of implant material and implant design is highly dependent on individual needs and the patient's pre-existing condition. This includes functional status and the anatomical and biomechanical properties of the individual knee (94). As wear of the PE inlay is a significant concern, the development of implant designs has led to an optimization of wear resistance and biomechanics and consequently has reduced the number of revision surgeries caused by PE-wear (93).
The indications dictate the type of implant necessary to achieve the best possible result for the patient. The different types can be distinguished as follows: (21, 94, 97)

- Unicompartmental knee replacement
- Bicompartmental knee arthroplasty/total condylar arthroplasty with/without patellar resurfacing
    - Cruciate retaining
    - Cruciate sacrificing
        - Posterior stabilized knee
        - Anterior stabilized knee
- Constrained non-hinged
- Constrained hinged

4.5.1 Unicompartmental knee arthroplasty

Although the vast majority of patients today receives a TKA implant unicompartmental knee arthroplasties (UKA) in the patellofemoral, medial or lateral compartment are currently used in approximately 8% of cases (8). UKA's superiority against TKA has been suggested in terms of optimized functional outcome, fewer medical complications, lower postoperative length of in-patient stay and greater cost-effectiveness (98-100). Higher revision rates and subsequent surgeries to implant TKA, in case the other compartments develop OA as well, demonstrate notable arguments against a wider implantation of UKA (8, 97).

4.5.2 Total condylar arthroplasty, Bi-/Tricompartimental knee arthroplasty

Bicompartmental knee arthroplasty refers to the resurfacing of two compartments, mainly the medial and lateral, representing total condylar arthroplasty. The ACL usually has to be removed while the remaining capsule and ligaments are the primary stabilizers. The PCL either can be retained (cruciate retaining) or has to be removed (cruciate sacrificing/posterior stabilized), depending on the implant design (94). These methods remain the two most widely used replacement options (8).
Proponents of either of the two options emphasize the advantages and disadvantages presented in table 4 (101-104). Nevertheless, literature suggests no significant difference between posterior stabilized and cruciate-retaining TKA regarding knee function, postoperative knee pain, and complication rates (104). One paper stated better flexion and range of motion in the posterior stabilized patient collectives but questions the clinical importance (105).

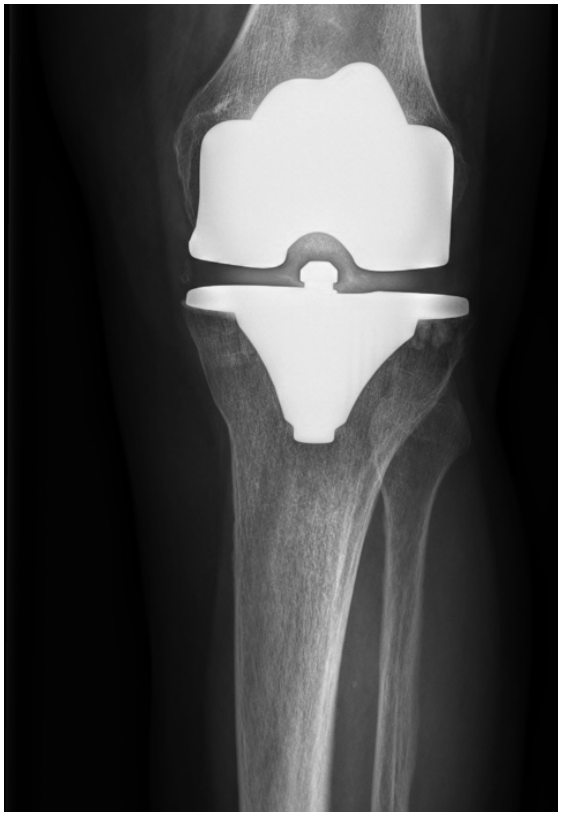

Figure 5. Example of a fixed bearing TKA in AP X-Ray. Implant design by Stryker®, Mahwah, NJ, USA.

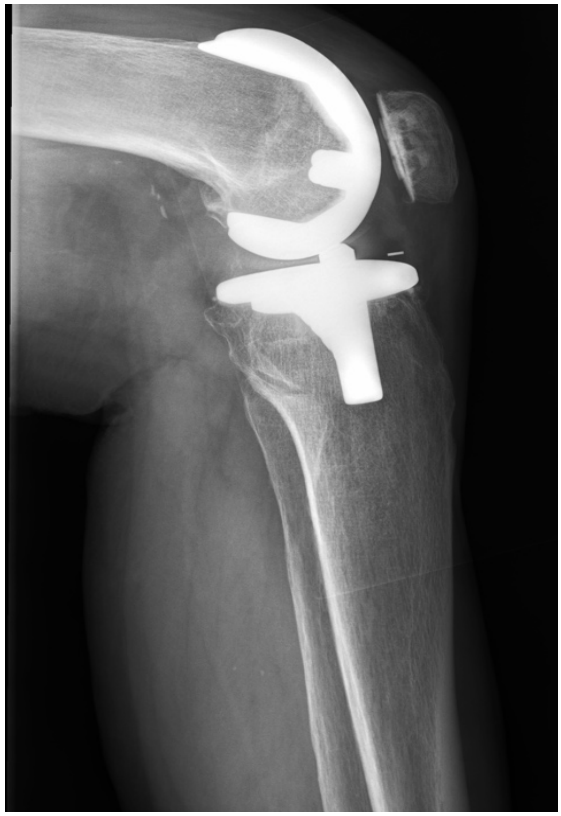

Figure 6. Example of a fixed bearing TKA in lateral X-Ray. Implant design by Stryker®, Mahwah, NJ, USA.

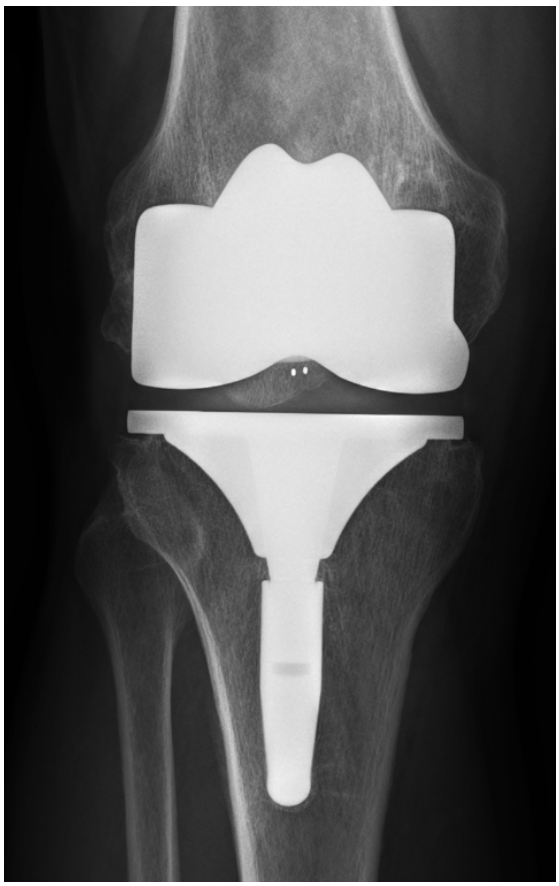

Figure 7. Example of a cruciate retaining TKA in AP view. Implant design by Implantcast, Buxtehude, Germany.

	Advantages	Disadvantages
Cruciate Retaining	- Inherent stability - Less load between bone & cement - Improved kinematics - Improved proprioception - Better implant stabilization	- Anterior knee pain - Sagittal laxity - Knee dysfunction - Tibial bearing damage
Posterior stabilized	- Conforming articulation - Better knee flexion - More predictable kinematics and reproducible rollback - Lower range of axial rotation and condylar rotation	- Anterior knee pain - Patella clunk syndrome - Tibial post fracture - Impingement - Breakage

Table 4. The advantages and disadvantages of cruciate-retaining and posterior stabilized TKA.

TKAs can further be subdivided into fixed- (FB) and mobile-bearing (MB) implant designs. The FB is attached to the tibial tray whereas the MB allows for movement between the bearing and the tray. During the MB's development the hypothesis was to improve PE wear and loosening of implant components (106). Earlier FB implants have had the problem of either having high conformity bearing surfaces with low contact-stress but high torque at the bony inserts or vice versa having low conformity bearing surfaces with less torque but high contact-stress (107). The MB provides both congruity and mobility to either reduce contact-stress and constraint force (108). The MB device's kinematic advantage is a better rotational capability between femur and tibia, resulting in a better gliding of patella and femur. The disadvantage is a higher risk of dislocation and instability because of better mobility (109).
Despite the hypothesized advantages the published data has not demonstrated any MB's superiority against the FB implants. Both designs show excellent results and survival. Therefore, it is an individual choice on which design to use (106, 109, 110).

4.5.3 Constraint TKA

The usage of non-constrained implant designs is dependent on soft-tissue stability and enough bone-mass to support the implant. If such implant designs seem not feasible pre- or intraoperatively, constrained designs may be used (111). Differentiation can be made into semi-constrained (Constraint Condylar knee/CCK) and constrained/hinged devices.

The CCK is based on the posterior stabilized design, whereas a longer PE stem is used to improve varus and valgus stability. Indications are revision surgeries and primary TKAs when the knee shows high instability and substantial deformation (94). The higher stabilization properties of CCK come at the cost of higher torque at the anchorage, hypothesized to lead to earlier implant loosening. Research could disprove this hypothesis and even determine a 96% survival after ten years (112). Additionally, routine implantation of CCK is recommended for complex primary situations (113).

The hinged design uses a connecting bar and usually rotating bearings to link the femur and tibia, producing a fixed extension stop (21). Modern hinged designs feature rotating hinges inserted in the tibial component to reduce torque on the bone and reduce the risk of implant loosening, which was especially problematic in earlier designs (94). Primary indications are complex revision surgeries and primary TKAs with severe varus or valgus, collateral ligament insufficiency, or relevant bone loss. Results vary widely, with reported 10-year survival rates of 51-92.5%. The same goes for complication rates of 9.2-63% (114).

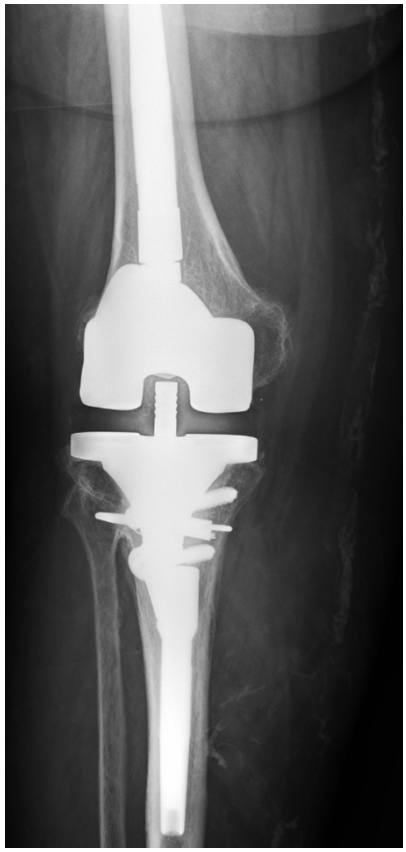

Figure 8. Example of a semi-constrained TKA in AP view. Implant design by Stryker, Mahwah, NJ, USA

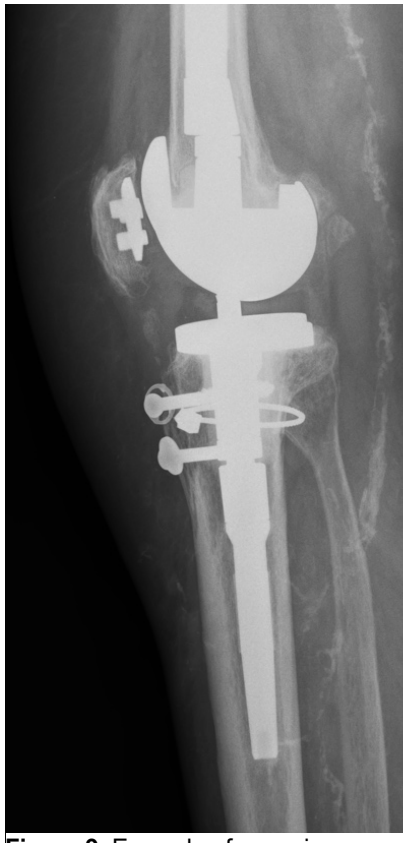

Figure 9. Example of a semi-constrained TKA in lateral view. Implant design by Stryker, Mahwah, NJ, USA

4.6 Alignment

To ensure the best possible outcome of TKA, surgeons have to ensure the best possible alignment of the different implant designs according to preset standards. For nearly three decades, the benchmark has been the mechanical alignment described by Insall, where a joint line should be created perpendicular to the mechanical axis. A biomechanical simplification allows for the even load distribution across the medial and lateral compartments: instead of a correct anatomical cut at 3° of varus at the tibia and 9° of valgus at the femur, the tibia and the femur are cut at 90° relatively to its anatomical axis and 4 to 6° of valgus in relation to its anatomical axis, respectively (115). Research has shown an increased force on the medial compartment and increased PE wear when adhering to the anatomical requirements (116-118).

Due to its high implant survivorship, this method has been established as a gold standard. Despite improvements in implant design and precision in surgery (i.e., navigation systems, patient-specific instrumentation, robotics), the functional outcome seems limited concerning dissatisfaction and residual symptoms (119, 120). Those technology-based assistive devices rather are in a developmental phase than widely implemented in implanting TKAs (121).

It has been hypothesized that a more kinematically (anatomically) aligned TKA would lead to less ligament release and better functional outcomes (36). Accordingly, there is an interindividual difference between anatomical and mechanical axes between patient groups, which requires a more individual approach to implant alignment (39). This hypothesis may be seen as a re-emergence, as earlier trials showed high failure rates due to limitations of the implant systems and high PE wear. More recent systems are more reliable, and recent literature suggests beneficial outcomes of kinematically aligned TKAs (122). Contradictory, Young et al. have shown no benefit in functional outcome and question the justification of taking the risk of implanting a kinematically aligned TKA in terms of long-time survival (123). More research is needed, but a more individual approach to implant alignment may be the key to improve functionality and patient satisfaction in the long term.

4.7 Complications and causes for revision

A revision rate of 3-5% for many TKA designs is generally reported over all registries (8). Literature contradicts itself in identifying the leading causes mentioning significantly different percentage values for the respective indications. This inconsistency may be due to different trial designs or different implant designs used during the trial. Therefore, registry databases provide a better foundation on which the causes for revision can properly be determined. Sadoghi et al. have found aseptic loosening, septic loosening (i.e., infection), pain, and wear to be the most frequent causes in this order (11).

Aseptic loosening seems to become relevant after a long period, whereas periprosthetic joint infection (PJI) is the leading cause for early revision (i.e., within the first 15 years) (124). The registries of New Zealand, Australia and Sweden similarly show an increase in early revision due to PJI (8). An attempt at an explanation for this occurrence is the combination of, one the one hand, increasing numbers of obesity and younger patients that receive TKAs and, on the other hand, that both obesity and younger age have been identified to be independent risk factors for the development of PJI after TKA (6, 76, 87, 125).

The outcome of TKA is generally considered satisfactory, although a survey from Sweden showed 8% dissatisfaction 2-17 years after primary TKA, which approximately doubled after revision surgery (126). Not surprisingly, revision surgery is associated with a higher risk of complications, a longer length of stay, unsatisfactory outcomes, and a relatively shorter implant survival compared to primary TKAs (127). Additionally, the risk of re-revision after revision is estimated to be four to five times higher further deteriorating the outcome (97). Apart from clinical measures, the economic burden of revision TKAs is enormous. In the US, estimations on revision surgery costs are 49.360$ for each surgery, additionally consuming significant resources and capacities (127).

As revision surgeries in total are increasing following the growing number of patients requiring TKA, the clinical and economic burden will rise significantly (127, 128). Furthermore, the younger and more active patient collective requiring TKA will substantially contribute to revising TKA (129).

After all, identifying the causes for revision and the predisposing risk factors for complications is vital for improved outcomes and reduced economic and clinical impact.

5 Tobacco Smoking

Tobacco smoking is probably one of the most evident occupational risk factors for developing debilitating diseases. Currently, the number of smokers globally is estimated at 1.3 billion people, with most smokers living in low- to middle-income countries (130, 131). The confirmation that cigarette smoking causes lung cancer is more than 50 years old (132). Twenty-five years ago, estimations suggested that 15% (one in seven cases) of cancer is caused by cigarette smoking (133). In 2000, more than one in every ten cardiovascular deaths worldwide (1.62 million) was attributable to tobacco smoking (134). In 2017 smoking ranked as the second leading risk factor for both death and DALYs (disability-adjusted life years), with smoking-attributable deaths having increased by 24.9% from 1990 to 2017 (14). During the same period, the percentage of all-cause all-age deaths due to smoking decreased in high SDI countries, whereas it increased in the countries with a lower SDI (14). In the 21st century, an estimated one billion people will die due to tobacco smoking (130). Smoking's tremendous impact on public health does not stop at causing disabling diseases, but it also negatively influences surgical procedures. A wide range of complications attributable to tobacco smoking has been identified, including pulmonary complications, surgical-site infections, and death (135-137).
Several pathways responsible for developing diseases and complications have been identified. Cigarette smoke is a complex mix of more than 7000 chemicals, of which some act as cardiotoxins and 69 as identified carcinogens (138, 139). Smoking cessation programs have proven tremendously beneficial in reducing and reversing devastating effects of smoking on health. Not only do former smokers have a reduced risk of developing cardiovascular diseases (CVDs) in comparison to active smokers, but they also have better pre-existing conditions to better cope with the demand of surgeries (140-142).

5.1 Health risks

The health risks caused by tobacco smoking are numerous, including nicotine's neurotoxicity, cancer development – of which lung cancer is the most prominent one - , respiratory and CVDs, and adverse effects on the reproductive system (132). Additionally, metabolic and immunological changes have been observed (132). Those effects are not only restricted to active smoking but passive smoking as well,

bringing a particular focus on smoking's health risks regarding non-smokers (132) A full description of the all pathophysiological pathways and effects on every organ system and disease would go beyond this paper's scope, and focus will lie on the most prominent physical consequences of tobacco smoking.

5.1.1 Nicotine

Nicotine is the chemical agent responsible for addiction to tobacco products (143). Nicotine addiction is dependent on the dose of the nicotine delivered and the way it is delivered (144). As nicotine is a highly bioactive compound, it was hypothesized that it could promote cancer: nicotinic receptors are not only found in the brain but throughout the body, triggering several cellular pathways involved in carcinogenesis (145). Angiogenesis is considered vital for cancer survival and metastasis. Nicotine stimulates various processes to promote angiogenesis (i.e., endothelial cell migration, proliferation, and survival) (145). However, studies showed no cancer promoting effects but suggested an attenuating effect of nicotine on the cigarette smoke's cytotoxicity (146). A definite association between nicotine and cancer cannot be made due to insufficient data (132).

Nicotine promotes the release of catecholamines and other neurotransmitters, both provoking cardiovascular and metabolic effects (elevated heart rate, blood pressure, and cardiac output; lipolysis), suggesting a negative influence on the development of CVDs (138, 147). Comparisons between cigarette smoke and smokeless tobacco products have concluded that other constituents of tobacco smoke, apart from nicotine, are responsible for CVDs, not nicotine itself (138). Therefore, nicotine is seen as the driving factor for initiating and maintaining addiction and consequently provoking CVDs (138).

5.1.2 Pathophysiological effects on the cardiovascular system

Active tobacco smoking. Tobacco smoking is a major risk factor for developing many CVDs. Notably, it has a more significant impact on acute, thrombotic events than on atherogenesis itself (148). Current cigarette smokers have considerably higher odds of myocardial infarction (MI) (odds ratio [OR]: 2.95, 95% CI 2.77-3.14, $p<0.0001$) than never-smokers (149). The relative risk of cardiovascular events is generally higher for younger than older smokers, as – usually – such events are

rarer in young non-smokers than in old non-smokers (132, 149). Death from stroke is twice as likely in smokers than in non-smokers and former smokers, and smokers treated for coronary artery disease have a higher risk of sudden cardiac death (150, 151).

The number of cigarettes smoked per day over years may indicate the risk of developing CVDs, as the association between CVDs and tobacco smoking is nonlinear (152). Shallow levels of cigarette consumption (i.e., 1-4 cigarettes per day) increase the risk of dying from coronary heart disease almost threefold (153).

Cigarette smoking is an established risk factor for peripheral arterial disease (PAD), where, on the contrary to the above mentioned, a dose-response relationship between smoking and PAD has been observed, with two- to threefold higher odds of PAD than non-smokers (132, 154).

Smoking acutely raises blood pressure, but no clear association between smoking and hypertension is observable (155). Interestingly, smoking acts in a multiplicative manner with other cardiovascular risk factors. When combined with another risk factor, the multiplicated risk is generally higher than both risk factors added together (138). For example, smoking exacerbates the influence of systolic blood pressure on the risk of hemorrhagic stroke (156).

Tobacco smoking has been identified as the most significant modifiable risk factor for developing abdominal aortic aneurysms (AAA). By causing early atherosclerotic lesions in the abdominal aorta, tobacco smoking provokes AAA formation and progression (132, 138).

Exposure to second-hand smoke. Exposure to second-hand smoke (SHS) is associated with an increased risk for CVDs and stroke, confirmed by two large meta-analyses nearly ten years apart (157, 158). Interestingly, the confirmed risk for non-smokers exposed to SHS is out of proportion compared to active smoker's risk. SHS is mainly derived from the sidestream smoke from the cigarette's lit end and is qualitatively different and far more toxic than the mainstream smoke inhaled by active smokers (138).

Pathophysiology. Cigarette smoke is a complex compound of over more than 7000 toxic chemicals. These constituents provoke the critical aspects of the pathogenesis of smoking-induced CVD (132):

- endothelial dysfunction
- prothrombotic effect
- inflammation
- altered lipid metabolism
- increased demand for myocardial oxygen and blood
- decreased supply of myocardial oxygen and blood

Key constituents are the free radicals and reactive oxygen species, causing endothelial dysfunction and platelet activation, and early atherosclerosis by oxidizing low density-lipoproteins (159).

5.1.3 Pathophysiological effects on the respiratory system

Active tobacco smoking. Tobacco smoking adversely affects the respiratory system in many ways and confers the risk of dying from respiratory disease. The Global Burden of Disease Study 2017 estimated the global prevalence of COPD at about 299 million cases (2). Its high prevalence makes it one of the leading causes of morbidity and mortality, ranking third among the global age-standardized death rates for both sexes (3.2 million deaths) (160). Tobacco smoking is the primary cause of developing COPD and its comorbidities and may also promote the onset of exacerbations (161, 162). As the proportion of actively smoking women is growing, the number of female COPD-related deaths has surpassed male death-counts (132).

Emerging data suggest that smoking is a key aspect of promoting the onset and exacerbation of other respiratory diseases than COPD and lung cancer. Smoking may play a vital role in developing asthma and idiopathic pulmonary fibrosis and has been identified to increase susceptibility to tuberculosis infection, disease, and mortality (132). Additionally, smoking is a risk factor for developing both community-acquired pneumonia and invasive pneumococcal disease (163).

In general, respiratory symptoms (i.e., cough, phlegm, rhinitis) occur more often in smokers than in non-smokers, whereas smoking cessation significantly reduces

those symptoms (163). As for lung function in general, smoking is a fundamental contributor to decreased FEV_1. It reduces growth velocity during adolescence, causes an earlier onset of FEV_1 decline, and accelerates the decline of FEV_1 in the elderly (163).

Exposure to second-hand smoke. Children exposed to second-hand smoke have an increased risk of sudden infant death syndrome, acute respiratory infections, ear problems, asthma, respiratory symptoms, and slower lung growth (162). Adult non-smokers have an increased risk of developing lung cancer and probably COPD, but data is insufficient to infer a causal relationship between SHS and COPD (163).

5.1.4 Pathophysiological effects on cancer development

Lung cancer. Due to its nearly 70 confirmed carcinogenic constituents, tobacco smoking is a leading cause for developing neoplastic diseases (132). The list of neoplasms having a causal relationship with tobacco smoking is increasing, currently led by lung cancer. Over fifty years ago, lung cancer was discovered to be associated with tobacco smoking. Today, tobacco smoking is the primary cause of lung cancer (132, 164). Lung cancer is the most common cancer, with approximately 1.8 million new cases per year. Furthermore, it accounts for 20% of all cancer deaths (estimations are at 1.59 million deaths per year), thus being the most common cause of cancer death (163, 165, 166). The risk of developing lung cancer rises proportionately to the cigarette consumption per day, as well as the total duration of smoking (167). The number of years of tobacco smoking is more critical than consumed cigarettes per day. Therefore, a better variable to assess smoking risk is to calculate the pack-years (163).

Other cancers. Tobacco smoking is responsible for 30% of all cancer deaths globally. Other cancers, including lung cancer, being causally linked to tobacco smoking, are noted in table 5 (132). Regarding breast cancer, insufficient data is available to link it to tobacco smoking causally, but the data available is highly suggestive (132).

Oropharynx	Liver
Larynx	Pancreas
Esophagus	Kidney
Trachea	Ureter
Bronchus	Cervix
Lung	Bladder
Acute myeloid leukemia	Colorectal
Stomach	

Table 5. Cancers causally linked to tobacco smoking.

5.2 Problems in surgery

Surgery in general. As described above, the diseases and their sequelae caused by smoking are numerous and debilitating, possibly leading to severe health restrictions and death. However, tobacco smoking does not only promote the development of new diseases but also adversely affects existing cardiovascular and respiratory diseases. These adverse effects are also apparent intra- and postoperatively (135).

Consequences of smoking on surgical outcomes relate to the toxic effects of acute smoke inhalation and chronic cumulative exposure. Smoking has been identified to cause tissue hypoxia, a driving mechanism for delayed wound healing and consecutively also infection, immediately as a response to smoke inhalation, remaining low for 30 to 50 minutes (168). Additionally, fibroblasts are stimulated to produce a stress response, resulting in an inappropriate buildup of connective tissue, possibly leading to delayed wound healing (169). Activation of the inflammatory system in response to the toxins and particles in tobacco smoke may destroy alveoli and reduce the surface area for gas exchange, providing predispositions for postoperative pneumonia and respiratory failure (170). Furthermore, tobacco smoke may lead to an increased bacterial load and delayed bacterial clearance, as shown in a study of mice infected with Pseudomonas aeruginosa (171).

Hawn et al. compared the surgical complications of non-smokers, prior smokers, and current smokers. A total of 393.794 patients from 8 major surgical subspecialties was available for analysis. Compared with non-smokers and prior smokers, current smokers had an increased risk of major respiratory complications (i.e., failure to wean, pneumonia, reintubation), surgical-site infection, and death.

These findings apply to all subspecialties. They also concluded a dose-response relationship, stating a significantly increased risk of complications for patients with more than 20 pack-years (current and prior smokers) (135). For former smokers, respiratory complications seem to diminish with more extended periods after quitting (172). Previous studies focusing on specific surgeries or related subspecialties have similar conclusions (136, 173, 174).

Orthopedic surgery. As mentioned above, OA is a highly prevalent disease, ultimately resulting in TKA. As smoking remains a widespread occupational habit, estimations of active smokers among TKA or total hip arthroplasty (THA) patients range between 10% and 24% (175). Smoking as a risk factor for surgical complications implies the hypothesis that specific complications in orthopedic surgery, especially TKA and THA, would more often be observed in smokers compared to non-smokers. Several studies have been conducted, confirming an association between tobacco smoking and surgical complications described above, as well as earlier time to revision surgery in case of smoking (15, 16, 137, 175, 176). Many of these studies focused on identifying short-term complications, namely deep-wound infections, cardiopulmonary complications, the requirement of postoperative intensive care, and mortality (16, 137, 175). Long-term complications in terms of earlier revision are indecisive. It has been mentioned that earlier time to revision was due to tobacco smoking (177). Singh et al. have conducted a systematic review including 21 studies and concluded an increased risk for postoperative complications and mortality for smokers among THA and TKA patients. However, they stated that more research was needed to determine an association of smoking with prosthetic loosening (178). In another study, Singh et al. confirm an increased risk for infectious complications, and they show an increased risk for adverse functional outcomes requiring revision arthroplasty (176).

5.3 Smoking Cessation

The lasting effects of tobacco smoking are sustained by continued cigarette consumption. Fortunately, studies have confirmed the tremendously beneficial effects of quitting. Smokers tend to lose a life-decade; however, those effects can almost be eliminated by smoking cessation before the age of 40 (164). Nevertheless, patients aged older than 70 also benefit from those mortality-reducing effects (179). Additionally, quitting is more effective than just reducing the number of cigarettes smoked (150, 153). Apart from mortality benefits, former smokers also reduce their risk of developing tobacco-associated CVDs, pulmonary diseases, and neoplasms (132).

After a cardiovascular event, continued smoking increases the risk of re-experiencing another cardiovascular event dramatically (i.e., myocardial infarction, stroke, death) (142). Smoking cessation also has positive effects on COPD - reducing lung function decline and the odds of exacerbation - and lung cancer - reducing the risk of recurrence, development of a second primary cancer, and mortality (142).

As for surgical complications, smoking cessation is generally recommended based on studies identifying the risk (135, 175). However, suggestions are to define the ideal intervention time to provide better short-term and long-term outcomes (176). Thomsen et al. concluded in a Cochrane review that the current evidence supports that active smokers should be offered intensive interventions, including behavioral support and pharmacotherapy, prior to surgical procedures. Those interventions have proved beneficial for changing smoking behavior postoperatively and may also reduce the incidence of complications. A definite timing could not be determined, but the authors suggested at least four weeks prior to the procedure (180).

Despite the evidence that smoking cessation is beneficial, it is difficult for many smokers to quit smoking. Treatment approaches to aid in smoking cessation are available and can help smokers quit. Cessation programs primarily are planned for the individual smoker, who wants to quit, but may also be aided by public measures. Individual treatment approaches fall into two categories: psychosocial counseling and pharmacotherapy (162). The combination of both has been found to enhance success (181). Clinical practice guidelines recommend using pharmacotherapy and identify three strategies: nicotine-replacement therapy, bupropion, and varenicline (162).

Additionally, public options may help to increase cessation rates and to drop the rate of new smokers. Approaches mentioned in the literature are higher prices for cigarettes by increased taxes, restriction on smoking in public places, bans on tobacco advertising, education, and easy access to cessation efforts (130, 164).

6 Aim of the study

Previous studies have found smoking to be one of the most important modifiable risk factors affecting human health. In combination with TKA being a delicate and technically demanding procedure, the burden on patients increases. Previous studies have concluded that smoking diminishes short- and long-term outcomes. Such a study has not been conducted in Austria before despite Austria being a high prevalence country concerning both smoking and TKA.

Knowledge of how smoking affects the outcome of TKA in an Austrian clinic could provide the experience necessary to convince patients of smoking cessation and improve the outcome of TKA. The aim of this study was to identify smoking as an independent significant risk factor for TKA in an Austrian clinic.

The hypothesis was that patients who receive a TKA and smoke have an earlier time to revision surgery and an overall higher complication rate. Additionally, this study included secondary findings regarding clinical function after TKA among smokers.

7 Materials and Methods

For this retrospective analysis, a pre-existing study cohort was evaluated, including patients who received a primary TKA at the Department of Orthopedics and Orthopedic Surgery at the LKH Radkersburg, Austria, between 2003 and 2006.

Regular follow-ups – either by clinical examination or by telephone call - are intended to ensure satisfying results and detect potential complications. Follow-ups were performed at the Department of Orthopedics and Orthopedic Surgery at the LKH Radkersburg, Austria, and the Department of Orthopedics and Trauma, Medical University of Graz, LKH Univ.-Klinikum Graz, Austria. Both hospitals are part of the KAGes (abbreviation for Steiermärkische Krankenanstaltengesellschaft m.b.H.), which provides the same patient organizing system (MEDOCS) across its hospitals. Therefore, it was possible to search for specific patient data retrospectively. Nursing staff consistently ascertains smoking status at admission for patients at all KAGes hospitals, including type of product (cigarette, cigar, pipe) and number of specific products consumed in a day.

For patients included, the potential follow-up period was up until 2020, with the date of last follow-up and time to last follow-up ascertained in each case. The predictor of interest was smoking status at time of surgery, including active smoking, former smoking, and never smoking.

The primary outcome of interest was any complication for which revision surgery became necessary during the follow-up period. The secondary outcome of interest was assessment of functional status, utilizing the clinical scores Knee Society Score (KSS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Short Form 12 Physical and Mental Health Composite Scores (SF-12PCS and SF-12MCS). Pain Visual Analogue Scale (VAS) pre-and postoperatively facilitated pain evaluation and improvement.

Additional variables were time to last follow-up from date of surgery, time from primary TKA to revision for implant-related causes, and gender, for which differences were also calculated.

7.1 Clinical Outcome

TKA may be evaluated solely by documenting revision and complication rates. However, evaluation of TKA has improved over time by incorporating patient-reported outcome measures (PROMs) and objectified scores. Several measures are available, of which the KSS, WOMAC, SF-12PCS and SF-12MCS, and the VAS were used. In a review by Harris et al., in which 32 shortlisted measures were reviewed for the quality of their measurement properties, WOMAC was among the best performing condition-specific PROMs, and SF-12 was the best performing generic measure (182). Since the adoption of PROMs, these instruments have shown a beneficial effect of TKA in terms of quality of life for most patients (9). However, with 15-20% of patients reporting dissatisfying results after TKA, the importance of implementation of such instruments in addition to traditional assessments during follow-ups after surgery (i.e., assessing complication and revision rates) is highlighted (10). For assessing pain, a wide variety of rating scales is available, of which the VAS is a widely used measurement in diverse adult populations due to its simplicity and adaptability (183).
The KSS has been added for gathering objective information on outcome after TKA, being the most popular method of evaluating TKA surgeries worldwide due to its simplicity and wide adoption (184).

Visual Analogue Scale. The VAS is a unidimensional scale consisting of a horizontal or vertical line, usually 100 millimeters in length. On each end of the line, verbal instructions describe either extreme (i.e., “no pain” and “worst imaginable pain”). Usually, the recall period is the current situation or the last 24 hours. The patient is asked to mark any point on the line reflecting the current pain condition. The score may be determined afterward and interpreted, whereas higher scores indicate more pain (183).

Western Ontario and McMaster Universities Osteoarthritis Index. The WOMAC has initially been developed for hip and knee OA for evaluating clinically significant changes in health status following treatment. It then has been validated for its use in OA patients undergoing TKA. The WOMAC evaluates pain, stiffness, and physical function with 5, 2, and 17 questions, respectively. Maximum scores for each subscale are 20, 8, and 68, with lower scores indicating worse outcomes (185).

Various adoptions are obtainable. This study cohort was evaluated using a modified WOMAC score based on the work of Roos et al. (186), in which additional questions (9, 7, and 17, respectively, according to the scheme mentioned above) were merged with the original WOMAC score. Each question had to be answered from 0 – 4, whereas 0 being extreme disabilities and 4 being no symptoms. The achieved score then is translated to a scale from 0 – 100, whereas 0 being severe disability and 100 being no symptoms (186). The questionnaire is self-administered and can be completed in 5 to 10 minutes.

Short-form 12. The 12-item short-form health survey (SF-12) is a generic questionnaire for evaluating patient-based quality of life. It is derived from the 36-item short-form health survey (SF-36) and comprises physical and mental health (Physical Component Summary, PCS; Mental Component Summary, MCS) in 12 questions. Its use has been validated and compared to the SF-36, where the SF-12 has shown considerable accurateness with far less respondent burden (187, 188).

Knee Society Score. The original Knee Society Clinical Rating System was developed as a simple but objective scoring system consisting of two parts. The knee is assessed for pain, stability, and range of motion with maximum scores of 50 (pain-free), 25 (stable knee), and 25 (maximum range of motion 125°), with deductions for flexion contracture and extension lag. Stair climbing without help and unlimited walking distance are awarded 100 points, with deductions when utilizing walking aids (184, 189).

The original rating system has been refined to balance objective and subjective ratings and to combine them into one scoring system. Additionally, the younger patient population's expectations, satisfaction, and physical activities should be better characterized using the new scoring system (184).

Part of this study cohort was evaluated using the original rating system due to its validity, simplicity, objectivity, and the fact, that the enhanced rating system is relatively novel.

7.2 Patient Collective

For this study cohort, the exclusion criteria were the following:

- Primary TKA before 2003
- Revision TKA between the years 2003 and 2006
- No smoking status available
- Double entries
- No patient data available in MEDOCS

Seven hundred eight patients were initially included in the study cohort. After checking for exclusion criteria, data of 681 (n=681) patients was gathered for statistical analysis. Of those, 478 (70.2%) were female, and 203 (29.8%) were male. Mean age at time of surgery was 68.4 years (±8.9 years). Smoking status was defined as current smokers, former smokers, and never smokers.
For 466 (68.4%) patients, data of WOMAC and SF-12PCS and SF-12MCS was accessible. For 469 (68.9%) patients, data of KSS knee and KSS function was accessible. 470 (69.0%) patients were assessed for pain pre-and postoperatively via the VAS. (Table 9)

7.3 Statistical Analysis

All statistical analyses were performed using Stata® Version 16 (StataCorp LLC, Texas, USA). Continuous variables are reported as means and standard deviations or medians with the lower (Q1) and upper (Q3) quartile, where appropriate. Discrete variables are presented as proportions and percentages. For the comparison of discrete variables, the chi-squared test for proportions was used. For the analysis and comparison of mean values of binominal data and continuous data, a two-sample, unpaired t-test was used. A p-value of less than 0.05 was considered statistically significant.
Notably, regarding functional status, the scores and measurements had not been gathered for all patients, wherefore separate statistical analyses were done, using the smaller study cohort only.

8 Results

In total, 681 patients treated for OA and having received a primary TKA were evaluated and included in statistical analyses.

Forty-six (6.8%) patients were current smokers, 39 (5.7%) were former smokers, and 596 (87.5%) were never smokers. Of the smokers, 26 (56.5%) were female, and 20 (43.5%) were male. Of the former smokers, 10 (25.6%) were female, 29 (74.4%) were male. In an adjusted analysis, active smokers were more likely to be male than female (p=0.010) compared to never smokers, and more men were former smokers than women (p<0.001). The relative proportion of active smokers against former smokers was significantly higher in women than in men (p=0.004). The mean age at the time of surgery was significantly lower in active smokers with 57.0 years (p<0.001) and former smokers with 63.3 years (p<0.001) compared to never smokers with a mean age of 69.6 years. Additionally, compared to active smokers, former smokers showed a significant increase in age at time of surgery (p=0.015). (Table 6)

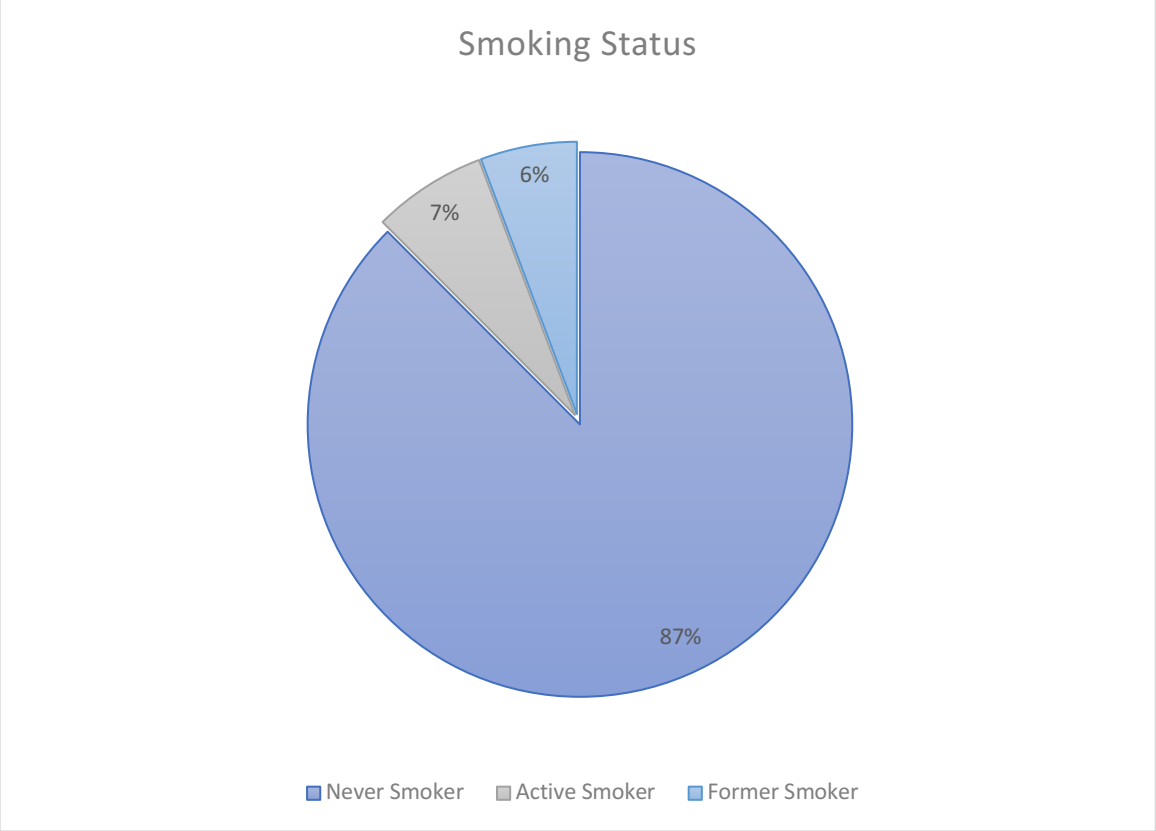

Figure 10. Chart illustrating the proportions of the smoking status groups.

	Active smoker (n=46) N (%) SD (±) 95% CI	Never smoker (n=596) N (%) SD (±) 95% CI	p	Former smoker (n=39) N (%) SD (±) 95% CI	Never smoker (n=596) N (%) SD (±) 95% CI	p	Active smoker (n=46) N (%) SD (±) 95% CI	Former smoker (n=39) N (%) SD (±) 95% CI	p
Male	20 (11.5%)	154 (88.5%)	**0.010[a]**	29 (15.8%)	154 (84.2%)	**<0.001[a]**	20 (40.8%)	29 (59.2%)	**0.004[a]**
Female	26 (5.6%)	442 (94.4%)		10 (2.2%)	442 (97.8%)		26 (72.2%)	10 (27.8%)	
Age surgery	57.0 (±9.7)	69.6 (±8.2)	**<0.001[b]**	63.3 (±7.7)	69.6 (±8.2)	**<0.001[b]**	57.0 (±9.7)	63.3 (±7.7)	**0.015[b]**

Table 6. Gender and mean age at time of surgery in relation to smoking status.
[a] Chi-squared test, [b] two-sample t-test with equal variances, *95% CI* 95% Confidence Interval, *Age surgery* mean age at time of surgery, ***bold*** statistically significant p-value (<0.05)

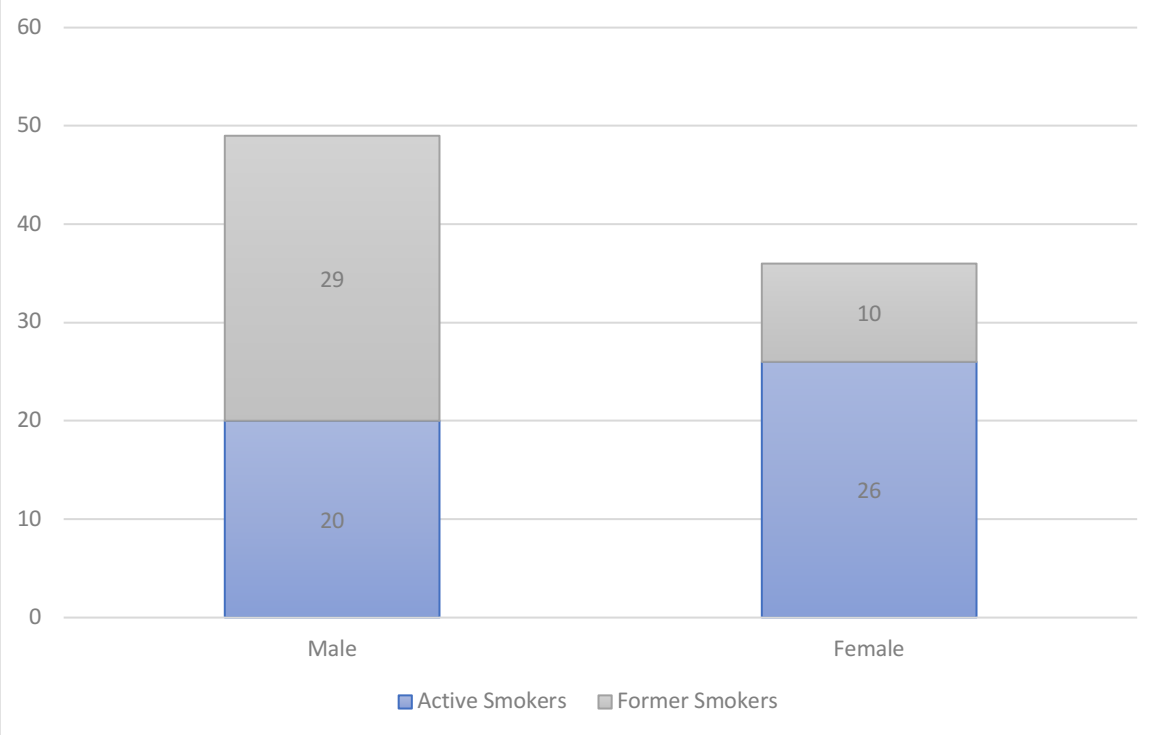

Figure 11. Chart illustrating the different proportions of active smokers and former smokers with respect to gender**.**

8.1 Revisions and complications

The majority of endoprosthesis systems used was ACS® Knee System (Implantcast, Buxtehude, Germany; 540 implantations, 79.3%), followed by Scorpio® Knee System (Stryker Orthopaedics, Mahwah, NJ, USA; 138 implantations, 20.3%), and AMC MkII™ (Corin, Eisenstadt, Austria; 3 implantations, 0.4%).

Minimum noted follow-up time was within the first month (zero months) postoperatively (13 days) and median follow-up time was 117 (Q1=59, Q3=126) months. In total, 126 (18.5%) complications were observed, of which 57 (45.2%) were mechanical complications, 69 (54.8%) were soft-tissue complications. In 124 (18.2%) patients, complications led to revision surgery. Median time from primary TKA to revision was 25 months (Q1=12, Q3=51). In 2 (0.3%) patients, complications did not lead to revision surgery because conservative management was successful.

For the overall revision likelihood, no statistically significant difference between active smokers (13/46, 28.3%) and never smokers (103/596, 17.3%) could be shown (p=0.062). However, a tendency towards active smokers having a higher risk of revision surgery than never smokers was present without statistical significance. Moreover, there was no difference between former smokers (8/39, 20.5%) and never smokers (103/596, 17.3%; p=0.607), as well as former smokers and active smokers (p=0.409) regarding any revision.

For soft tissue complications, a significant difference between active smokers (9/46, 19.6%) and never smokers (56/596, 9.4%) was notable (p=0.028). For former smokers and never smokers (p=0.859) and former smokers and active smokers (p=0.235), no such significance was apparent. Regarding mechanical complications, neither active smokers compared to never smokers (p=0.910), nor former smokers compared to never smokers (p=0.656), or former smokers compared to active smokers (p=0.806), revealed any statistically significant difference. (Table 7)

	Active smoker (n=46) N (%)	Never smoker (n=596) N (%)	p*	Former smoker (n=39) N (%)	Never smoker (n=596) N (%)	p*	Active smoker (n=46) N (%)	Former smoker (n=39) N (%)	p*
ST comp.	9 (19.6)	56 (9.4)	**0.028**	4 (10.3)	56 (9.4)	0.859	9 (19.6)	4 (10.3)	0.235
Mech. comp.	4 (8.7)	49 (8.2)	0.910	4 (10.3)	49 (8.22)	0.656	4 (8.7)	4 (10.3)	0.806
AL	2 (4.4)	27 (4.5)	0.954	4 (10.3)	27 (4.5)	0.108	2 (4.4)	4 (10.3)	0.289
Infection	2 (4.4)	22 (3.7)	0.821	3 (7.7)	22 (3.7)	0.213	2 (4.4)	3 (7.7)	0.514
RM	5 (10.9)	20 (3.4)	**0.011**	1 (2.6)	20 (3.4)	0.789	5 (10.9)	1 (2.6)	0.136
PF	1 (2.2)	13 (2.2)	0.997	0 (0.0)	13 (2.2)	0.351	1 (2.2)	0 (0.0)	0.354
Wear	1 (2.2)	8 (1.3)	0.644	0 (0.0)	8 (1.3)	0.467	1 (2.2)	0 (0.0)	0.354
WD	0 (0.0)	7 (1.2)	0.460	0 (0.0)	7 (1.7)	0.496	0 (0.0)	0 (0.0)	-
Haematoma	2 (4.4)	5 (0.8)	**0.027**	0 (0.0)	5 (0.8)	0.566	2 (4.4)	0 (0.0)	0.188
Luxation	0 (0.0)	2 (0.3)	0.694	0 (0.0)	2 (0.3)	0.717	0 (0.0)	0 (0.0)	-

Table 7. Comparison of complications depending on smoking status.

* Chi-squared test, ***bold*** statistically significant p-value (<0.05), *ST compl.* soft tissue complication, *mech. compl.* mechanical complication, *AL* aseptic loosening, *RM* restricted movement, *PF* periprosthetic fracture, *WD* wound dehiscence

Of one-hundred-twenty-six documented complications (18.5%), 33 (26.2%; 4.8% *of the whole study cohort, n=681*) were aseptic loosenings, 27 (21.4%; 4.0%) infections, 26 (20.6%; 3.8%) restricted movements, 14 (11.1%; 2.1%) periprosthetic fractures, 9 (7.1%; 1.3%) mechanical wears, 7 (5.6%; 1.0%) wound dehiscences, 7 (5.6%; 1.0%) haematomas, 2 (1.6%; 0.3%) luxations, and one (0.8%; 0.2%) non-further specified soft-tissue complication. Active smokers were more likely to have restricted movement and hematoma in comparison to never smokers, whereas no difference for any of the other complications was observed. (Table 7)

Regarding gender, hematoma was more likely to appear in males than in females (p=0.001). The remaining complications showed no significant tendency towards a specific gender, indicating gender may not be the predisposing factor, eventually increasing the risk for particular complications. (Table 8)

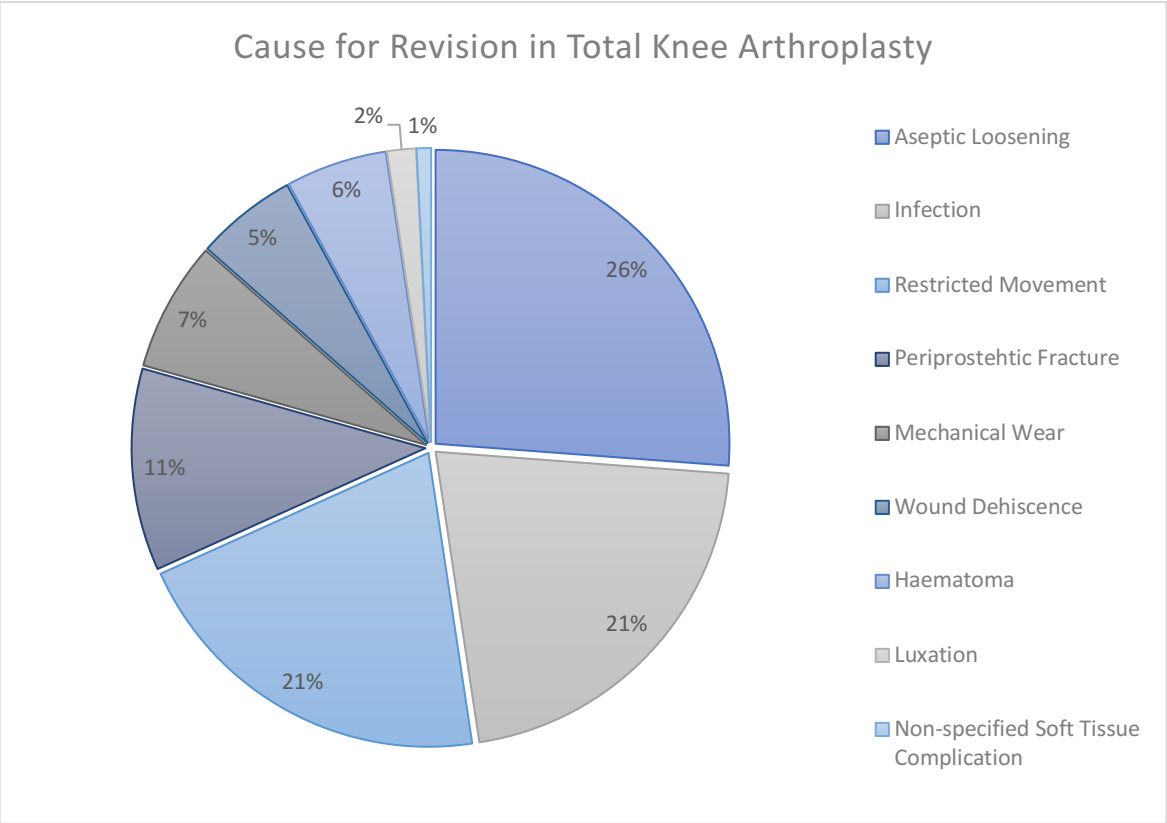

Figure 12. Diagram illustrating the causes for revision surgery after TKA in relative percentages with respect to the total number of revisions reported.

	Male (n=203) N (%)	Female (n=478) N (%)	p*
Aseptic loosening	13 (6.4)	20 (4.18)	0.229
Infection	9 (4.3)	18 (3.8)	0.683
Restricted movement	5 (2.5)	21 (4.4)	0.229
Periprosthetic fracture	6 (3.0)	8 (1.7)	0.281
Wear	2 (1.0)	7 (1.5)	0.616
Wound dehiscence	2 (1.0)	5 (1.1)	0.943
Haematoma	6 (3.0)	1 (0.2)	**0.001**
Luxation	0 (0.0)	2 (0.4)	0.356

Table 8. Influences of gender on specific complication risk.

*Chi-squared test, ***bold*** significant p-value (<0.05)

8.2 Clinical Outcome

Clinical-outcome data was collected in 466, 469, and 470 patients during follow-up. Clinical outcome was measured using WOMAC, KSS knee, KSS function, VAS preoperatively, VAS postoperatively, the mean reduction of VAS pre- to postoperatively, SF-12PCS, and SF-12MCS. (Table 9)

Smokers were more likely to score higher at KSS function (p<0.001) and SF-12PCS (p=0.0197) and to report higher pain ratings preoperatively (p=0.0031) compared to never smokers. The remaining scores were similar throughout all smoking status groups, indicating an overall positive outcome of TKA surgery regardless of smoking status (Table 9).

	Active smoker n† SD (±)	Never smoker n* SD (±)	p[a]	Former smoker (n=30) SD (±)	Never smoker n* SD (±)	p[a]	Active smoker n† SD (±)	Former smoker (n=30) SD (±)	p[a]
WOMAC	84.0 (±16.5)	80.1 (±15.5)	0.2127	86.2 (±13.4)	80.1 (±15.5)	0.0554	84.0 (±16.5)	86.2 (±13.4)	0.5583
KSS knee	84.8 (±14.2)	82.8 (±15.8)	0.4676	87.4 (±15.7)	82.8 (±15.8)	0.1213	84.8 (±14.2)	87.4 (±15.7)	0.4739
KSS function	79.4 (±24.2)	64.1 (±26.0)	**<0.001**	72.1 (±22.2)	64.1 (±26.0)	0.0994	79.4 (±24.2)	72.1 (±22.2)	0.2094
VAS pre.	8.3 (±1.2)	7.6 (±1.4)	**0.0031**	7.6 (±1.1)	7.6 (±1.4)	0.8651	8.3 (±1.2)	7.6 (±1.1)	0.0284
VAS post.	2.2 (±2.0)	1.9 (±2.0)	0.4214	1.3 (±1.7)	1.9 (±2.0)	0.1036	2.2 (±2.0)	1.3 (±1.7)	0.0640
VAS diff.	6.0 (±1.8)	5.6 (±2.3)	0.2935	6.3 (±2.1)	5.6 (±2.3)	0.1313	6.0 (±1.8)	5.6 (±2.3)	0.6201
SF-12PCS	41.2 (±10.9)	36.8 (±10.4)	**0.0197**	40.4 (±10.5)	36.8 (±10.4)	0.071	41.2 (±10.9)	40.4 (±10.5)	0.7674
SF-12MCS	53.2 (±10.5)	52.8 (±10.9)	0.8358	54.8 (±10.3)	52.8 (±10.9)	0.3268	53.2 (±10.5)	54.8 (±10.3)	0.5376

Table 9. Mean clinical scores in relation to smoking status.

* ***n=400*** WOMAC; ***n=401*** KSS function; ***n=402*** SF-12PCS, SF-12MCS; ***n=403*** KSS pain; ***n=404*** VAS pre., VAS post., VAS diff.

† ***n=34*** SF12PCS, SF12MCS; ***n=36*** WOMAC, KSS knee, KSS function, VAS pre. VAS post., VAS diff.

[a] two-sample t test with equal variances, ***bold*** statistically significant p-value (<0.05)

Regarding gender, significant differences were seen across all scores except pre-to-postoperative VAS difference and SF-12PCS (Table 10).

	Male n* SD (±)	Female n† SD (±)	p[a]
WOMAC	85.0 (±13.0)	79.7 (±16.2)	**<0.001**
KSS knee	87.4 (±11.6)	81.6 (±16.8)	**<0.001**
KSS function	73.0 (±24.4)	62.9 (±26.0)	**<0.001**
VAS pre.	7.4 (±1.4)	7.7 (±1.3)	**0.0313**
VAS post.	1.5 (±1.5)	2.1 (±2.1)	**0.0021**
VAS diff.	5.9 (±2.2)	5.6 (±2.3)	0.1549
SF-12PCS	38.8 (±10.5)	36.8 (±10.4)	0.0537
SF-12MCS	54.7 (±9.2)	52.2 (±11.3)	**0.0268**

Table 10. Mean clinical scores in relation to gender.

* ***n=132*** SF-12PCS, SF-12MCS; ***n=135*** WOMAC, KSS knee, KSS function; ***n=136*** VAS pre., VAS post., VAS diff.

† ***n=331*** WOMAC; ***n=332*** KSS function; ***n=334*** KSS knee, VAS pre., VAS post., VAS diff, SF-12PCS, SF-12MCS

[a] two-sample t test with equal variances, ***bold*** statistically significant p-value (<0.05)

9 Discussion

The aim of this study was to analyze whether smoking negatively influences the outcome of primary TKA. Statistically analyzing and comparing TKA specific complications as well as functional scores after primary TKA with regards to smoking status groups should provide information on how smoking influences the outcome after primary TKA.

Although our study group did not exactly replicate the findings from previously documented studies for any TKA-related revision surgery, a tendency towards an increased risk for revision in active smokers compared to never smokers could be found (15, 16, 137, 141, 175, 176). Our major finding was a significant increase in soft-tissue complication risk, which was apparent in the active smoker group. In contrast, the risk of infection was similar in both the active and never smoker groups, which does not comply with earlier findings from Moller et al., Duchman et al., and Singh et al. (16, 137, 175). In our cohort, primarily restricted movement and hematoma formation were significantly more common in active smokers as compared with never smokers. However, the incidence of these findings was relatively low, wherefore the clinical relevance of these findings remains to be questioned.

Interestingly, the percentage of active smokers at time of TKA-implantation was 6.8% in our cohort, compared to 10% to 24% of active smokers in primary TKA groups described previously (175). Additionally, with 18.2%, we observed a higher percentage of revision surgeries than across many registries of 3-5% at ten years (8). A possible cause may be the missing differentiation of short- and long-term complications, the potential longer than usual follow-up period of up to 17 years, and the inclusion of complications not traditionally defined as revisions, but also having been revised surgically, such as restricted movement. Eventually, the study cohort's high revision rate compared to registries could potentially be a coincidental finding or due to selection bias.

Confounding bias could be discussed as a possible cause for falsely lower revision rates in current smokers. For former smokers, the risk for revision was similar to the risk of never smokers. However, literature describes contradicting results, with Duchman et al. concluding that former smokers have an increased total complication risk compared to never smokers (137) and Lim et al. concluding that former smokers and never smokers have a similar complication risk (15).

Our study showed similar results regarding complication rates following primary TKA as described in a systematic review by Sadoghi et al. (11). We also found Aseptic loosening (21.4% of all complications) and infection (20.6%) to be the most predominant complications following surgery. However, in our study, the percentage of both complications is higher than described by Sadoghi et al. (29.8% and 14.8%). Therefore, we can affirm the impression that aseptic loosening and infection are crucial aspects following primary TKA surgeries that have to be considered during follow-up.

We found significantly more men to be active smokers, complying with current literature describing a higher percentage of male smokers than female smokers (132). Additionally, more men were former smokers, implying a higher rate of male smokers at any given time.

An interesting secondary finding was, that active smokers (57 ±9.7 years), as well as former smokers (63.3 ±7.7 years), had a significantly lower age at time of primary endoprosthetic knee surgery than never smokers (69.6 ±8.2 years). Similar results have been mentioned in the literature, indicating a particular need to investigate further why active and former smokers are at an increased risk of undergoing earlier TKA implantation (175-177).

Regarding clinical outcomes, interestingly, active smokers scored significantly better at KSS function and SF-12PCS postoperatively. Active smokers also reported higher pain ratings prior to surgery. A study from Matharu et al. found no clinically significant differences in patient-reported outcome measures between active smokers, former smokers, and never smokers, in-line with our findings (190). Future research should focus on more in-depth research of potential differences in clinical outcomes between the smoking status groups, as well as the investigation of reasons for differing outcome scores. We have no clear explanation of why active smokers score higher in specific functional outcome scores. However, we speculate that an overall decreased lifestyle level could have distorted the function-based scores as less physically active current smokers may not be as limited in their lifestyle as more physically active never smokers.

Gender differences

Our study found male patients to be at an increased risk of hematoma formation. However, with the sample size being small and with no significant gender

differences in other complication rates between male and female patients, we conclude an even overall complication risk following primary TKA regardless of gender. However, this does not comply with Singh et al.'s findings, implying higher rates of revision surgery and wound infections in men (191). Clinical outcome was significantly better in males for all scores except for the pre-to-postoperative VAS difference and SF-12PCS, indicating a favorable effect of primary TKA in male patients. In line with this, a review from O'Connor found that male patients reported lower pain ratings pre-and postoperatively and achieved better physical function than female patients (192). In our study, the differences were significant and complied with existing literature, but the absolute differences in scores are minor, wherefore the clinical significance remains debatable.

9.1 Limitations

This study has several limitations. First, we did not divide revisions and complications into early and late revisions or complications.

Second, the study cohort might not include enough patients to represent a proper sample size for active smokers. As mentioned above, with 6.8% of active smokers, our study cohort is below the previously mentioned rate of active smokers among TKA patients. This could either be due to the small sample size or incomplete reporting of actual smoking status at time of primary surgery. Related to this, obtaining smoking status was complicated as there was no standardized identification of patient records, although smoking status should be routinely ascertained at admission. Especially in Austria, with its high prevalence of active smokers, we can assume a higher rate of active smokers in a primary TKA study cohort than 6.8%. Moreover, we were also unable to obtain information on pack-years and cannot comment on dose-response on revision risk.

Third, we did not correlate our findings that active smokers present at an earlier age at time of surgery than never smokers. In light of this, additional research has to be done, correlating our preliminary findings with supplementary parameters, such as BMI, age, gender. All of these are known factors influencing time to development of OA and have to be considered when analyzing smoking status and an earlier age at the time of surgery, supposing that active smokers have an unhealthier lifestyle than non-smokers.

Fourth, no preoperative scores for KSS, WOMAC, and SF-12 were available, which would have provided insight into how the smoking status group would be different regarding pre-and postoperative functional improvement.

10 Conclusion

Our study highlights the need for further research on the effects of smoking on orthopedic surgeries, especially primary TKA. We could partly replicate the significant findings of earlier studies, and we could show a tendency of smoking being a risk factor of decreased outcome following TKA implantation. Future studies should include larger sample size and adjust for other confounding risk factors negatively influencing the success of primary implantation. At this moment, with our findings and the findings from earlier studies, we strongly recommend advising patients to discontinue tobacco smoking upon and after surgery to minimize complication risk.

11 References

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