Thesis

Evaluation of Neuropathic Pain after Total Knee Arthroplasty

submitted by

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Graz, 05.07.2023

Affidavit

I solemnly declare that I have independently and without any external assistance written the present thesis, that I have not used sources other than those indicated, and that I have clearly identified any passages taken verbatim or in substance from the sources I have used.

Graz, 05.07.2023 Danijel Colovic eh

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Glossary and Abbreviations

ACL	-	Anterior cruciate ligament
ANOVA	-	Analysis of variance
ATP	-	Adenosin triphosphate
AWMF	-	Working group of the scientific medical societies
P2X	-	ATP-gated purinergic channels
BDNF	-	Brain-derived neurotrophic factor
BKA	-	Bicompartmental knee arthroplasty
BMI	-	Body mass index
BTX-A	-	Botulinum toxin
CHEP	-	Contact heat evoked potential
CNS	-	Central nervous system
CPSP	-	Chronic postsurgical pain
CSF1	-	Colony stimulating factor 1
CSN	-	Cold sensitive neurons
CT	-	Computed tomography
DN4 Questionnaire	-	Douleur Neuropathique en 4 questions
DNMT	-	DNA methyltransferase
ECM	-	Extracellular matrix
FSQ	-	Fibromyalgia survey questionnaire
HADS	-	Hospital anxiety and depression scale
HCN	-	Hyperpolarization-activated, cyclic nucleotide-gated channel
HDAC	-	Histone deacetylase
IASP	-	International Association for the Study of Pain

ICRS	-	International cartilage repair society
IL	-	Interleukin
KCNA2	-	Potassium Voltage-Gated Channel Subfamily A Member 2
KAGes	-	Styrian hospital society
KV	-	Voltage gated potassium channel
KOOS	-	Knee Injury and Osteoarthritis Outcome Score
LANSS	-	Leeds Assessment of Neuropathic Symptoms and Signs
LEP	-	laser evoked potential
lncRNAs	-	long noncoding ribonucleic acid
miRNA	-	mini ribonucleic acid
MRI	-	magnetic resonance imaging
MS	-	Multiple sclerosis
NeuPSIG	-	Neuropathic pain special interest Group
ncRNA	-	Noncoding ribonucleic acid
NMDA	-	N-methyl-D-aspartate
NNT	-	Needed to treat
NRS	-	numeric rating scale
NSAR	-	Nonsteroidal antirheumatic drugs
PCL	-	Posterior cruciate ligament
PCS	-	Pain catastrophizing scale
PNS	-	Peripheral nervous system
PROM	-	Patient-Reported Outcome Measures
QST	-	Quantitive sensory testing

ROS	-	reactive oxygen species
SD	-	standard deviation
SF-36	-	Short form 36
SNARE	-	soluble N-ethylmaleimide-sensitive factor attachment protein receptor
SNI	-	spared nerve injury
SNRI	-	selective serotonin-norepinephrine reuptake inhibitor
TNF-α	-	tumour necrosis factor alpha
TCA	-	tricyclic antidepressants
TKA	-	tricompartmental/total knee arthroplasty
TRP	-	transient receptor potential channel
UKA	-	Unicompartmental knee arthroplasty
WOMAC	-	Western Ontario and McMaster Universities Osteoarthritis Index

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Zusammenfassung

Hintergrund

Die Knietotalendoprothese ist der Goldstandard in der Versorgung von Patient*innen mit Kniearthrose, bei denen konservative Therapieversuche gescheitert sind. Etwa 15% der Patient*innen entwickeln schlecht therapierbare chronische postoperative Schmerzen (CPSP). Risikofaktoren wie junges Alter, weibliches Geschlecht, neuropathische Schmerzen, vorbestehende chronische Schmerzen, Depressionen, und übermäßige Angst tragen zu schlechteren Ergebnissen bei. [1] Diese prospektive Studie setzte sich zum Ziel, herauszufinden, ob das postoperative Outcome unter Berücksichtigung dieser Faktoren vorhergesagt werden kann.

Methoden

Ein Kollektiv von 50 TKA-Patient*innen wurde einem präoperativen Screening unterzogen, das eine ausführliche Anamnese, klinische Untersuchung, sowie die Erhebung von mehreren PROMs wie den DN4, SF36, WOMAC, FSQ und HADS umfasste. Anhand der Ergebnisse wurden die Patient*innen in eine Hochrisiko- und eine Niedrigrisikogruppe eingeteilt. Um das klinische Ergebnis und die Entwicklung der CPSP zu vergleichen, wurden mehrere Nachuntersuchungen über einen Zeitraum von sechs Monaten durchgeführt.

Ergebnisse

Nach sechs Monaten zeigten sich signifikante Unterschiede in der NRS ($p < 0.001$), dem WOMAC ($p < 0.001$), sowie mehreren Untergruppen des SF36 (Schmerz $p < 0.001$, körperliche Funktionsfähigkeit $p < 0.001$, körperliche Rolle $p < 0.001$, Energie/Müdigkeit $p = 0.01$). In den Subgruppen Schmerz ($p = 0.027$) und Steifheit ($p < 0.001$) des WOMAC präsentierten sich signifikante Interaktionseffekte mit jeweils besseren Werten der Hochrisikogruppe. Die Ergebnisse des DN4 waren sowohl am ersten postoperativen Tag ($p = 0.005$), als auch nach sechs Wochen ($p = 0.041$) signifikant schlechter in der Hochrisikogruppe.

Schlussfolgerung

Die Hochrisikogruppe zeigte präoperativ und in der frühen Nachbeobachtung schlechtere Ergebnisse. Im Verlauf der Studie verbesserten sich ihre Ergebnisse und übertrafen nach sechs Monaten sogar die der Vergleichsgruppe in den WOMAC-Untergruppen Schmerz und Steifheit. Diese Ergebnisse legen nahe, dass präoperative neuropathische Schmerzen und andere Risikofaktoren zu einer schwierigeren frühen postoperativen Phase beitragen. Nichtsdestotrotz kann die TKA auch bei diesen PatientInnen zufriedenstellende Ergebnisse erzielen.

Abstract

Background

Knee osteoarthritis is a musculoskeletal disease that often leads to a permanent reduction of life quality. When conservative treatments fail, total knee arthroplasty is the current gold standard for alleviating patient suffering. About 15% of patients experience poorly treatable chronic postsurgical pain (CPSP). Factors like young age, female gender, neuropathic pain, pre-existing chronic pain, depression, excessive anxiety, and other yellow flags contribute to worse outcomes. [1] This prospective study aimed to preoperatively identify patients at disproportionate risk of developing CPSP, refining our understanding of the condition.

Methods

A group of 50 TKA patients underwent preoperative screening, including in depth anamnesis, clinical examination, and collection of PROMs such as the DN4, SF36, WOMAC, FSQ, and HADS. Based on the findings, patients were categorized into high-risk and low-risk groups. Follow-up assessments were conducted over a six-month period to compare clinical outcomes and CPSP development.

Results

ANOVAs performed after six months indicated significant improvements in subgroups of the SF36 (pain $p < 0.001$, physical functioning $p < 0.001$, role physical $p < 0.001$, energy/fatigue = 0.01), WOMAC (total $p < 0.001$, pain $p < 0.001$, stiffness $p < 0.001$, activity $p < 0.001$), and NRS in all subgroups ($p < 0.001$). Significant interaction effects between high-risk and low risk groups were found in the WOMAC subgroups of pain ($p = 0.027$) and stiffness ($p < 0.001$) at six months, showing better scores in the high risk group. DN4 scores remained significantly worse in the high risk group one day postoperatively ($p = 0.005$) and after six weeks ($p = 0.041$)

Conclusion

The high-risk group had worse preoperative outcomes, but over time, their results improved and even surpassed the comparison group in pain and stiffness subgroups of the WOMAC after six months. These findings suggest that

preoperative neuropathic pain and other risk factors contribute to a more challenging early postoperative period. Nonetheless, TKA can still yield satisfactory outcomes for patients with these conditions.

1 Introduction

Osteoarthritis of the knee is one of the most common musculoskeletal system diseases, especially in older age. With increasing life expectancy, the frequency of this clinical picture is likely to increase even further.

If conservative treatment attempts fail, surgical therapy by means of total knee arthroplasty (TKA) is today's gold standard to counteract the suffering of the patients. A completely pain-free postoperative course is rarely possible, but adequate pain therapy with the greatest possible pain reduction and the smallest possible drug side effects should be the goal. In particular, the development of CPSP in elective surgery should be avoided at all costs. However, not every patient requires the same therapeutic support, often making optimizing pain therapy difficult. This problem is particularly evident in the example of TKA, where about 15% of patients suffer from severe chronic pain postoperatively. [1]

The reason for this lies in an accompanying central sensitization, which causes additional burdensome neuropathic pain. Postoperative pain is usually classified as somatic pain. It results from activating tissue nociceptors due to intraoperative soft tissue damage. However, if nerves are relevantly injured, primarily peripheral sensitization develops, followed by central sensitization at spinal cord levels. This results in several things: The incoming stimuli from the wound area are less inhibited, thus amplifying and prolonging the stimulus amplitude. As a result, unpleasant plus phenomena such as increased pain perception (hyperalgesia) or even pain from normally nonpainful stimuli like touching (allodynia) can be triggered by short circuits in the afferent nervous system. The alteration of the pain pathways causes analgesics (non-steroidal anti-inflammatory drugs and opioids), which otherwise work well, to work poorly or not at all. From here on, different pain treatment with atypical analgesics, known as co-analgesics, is required. The use of antidepressants and anticonvulsants allows acceptable pain relief in some patients. Often, however, it takes a trial of therapy with different antineuropathic agents to achieve this goal. This neuropathic pain component represents one of the main causes of CPSP. The unpredictable development or sudden involvement of neuropathic pain, as well as its difficult diagnosis and analgesic adjustment, represent a real challenge for the affected patients and the treating physicians. [2]

However, by considering patient-specific factors, one can more likely predict the potential development of CPSP. There is already evidence that pre-existing chronic pain, prolonged use of analgesics, demographic factors such as young age and female gender, and psychological factors such as depression and excessive anxiety before surgery, among other yellow flags, worsen the outcome. [3] Other studies have shown that acute neuropathic pain in the first days postoperatively increases the risk of developing CPSP. [4]

1.1 Aim of this Study

Considering all this prior knowledge, different patient collectives (high risk, low risk), therefore, require different forms of pain management. If we recognize patients with increased risk early, it is also possible to intervene promptly and prevent the development of a CPSP.

1.2 Anatomy of the Knee

The knee joint ("articulatio genus") is the largest in the human body. [5] Mechanically, it is described as a modified hinge joint ("trochoginglymus"), allowing flexion and extension on a transversal axis as well as internal and external rotation on a longitudinal axis. [6] For the functionality of this complex and large joint to be given, a synergistic system of bony, ligamentous, tendinomuscular, and cartilaginous structures must work together. The structural basis of the knee is formed by three bony structures: the femur (thigh bone), tibia (lower leg bone), and patella (the largest sesamoid bone of the human body, which transmits the force of the quadriceps femoris muscle). [6]

These three bones combine to create a compound joint, with two joints formed between them. The tibiofemoral joint is formed by the medial and lateral condyles of the femur and the medial and lateral tibial plateaus. In contrast to the convex-shaped femoral condyles, the medial plateau exhibits a concave shape and the lateral plateau a convex shape. This leads to an incongruity, meaning that the normal alignment or congruence of joint surfaces is disrupted or misaligned,

potentially leading to functional impairment or instability, that is compensated by the two menisci (see Figures 1 and 2 and cartilage and menisci). [6–8]

The patellofemoral joint is created by the interaction between the facies patellaris femoris (femoral surface) and the facies articularis patellae (patellar surface). The femur forms a V-shaped groove that accommodates the patella, which articulates through its two facets: the medial and lateral facets. [5] The fibula does not act as a direct articular partner in the knee joint, but is connected to the tibia by a separate, taut joint. [6]

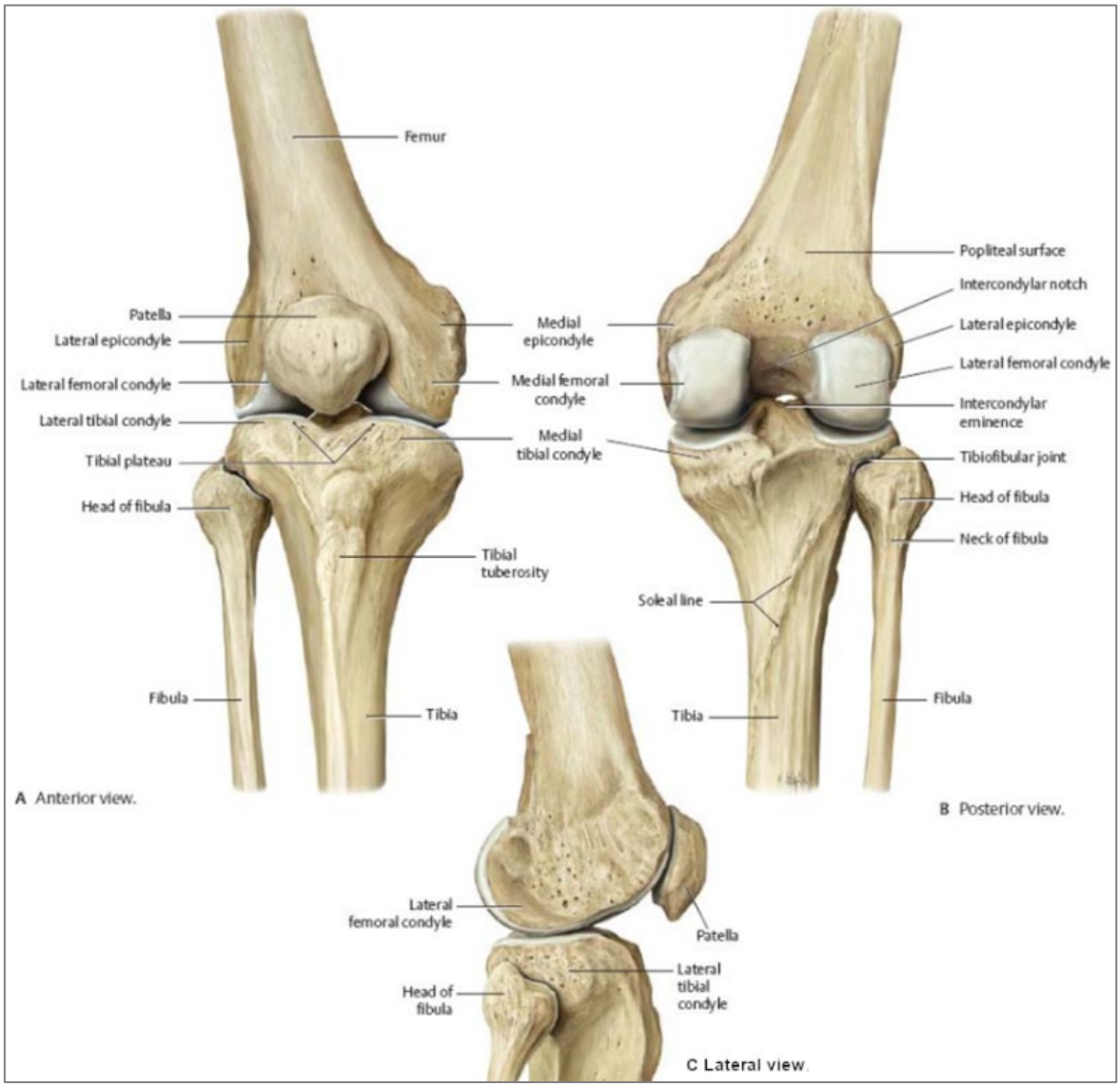

Figure 1: Showing the bony structures of the art. genus from anterior (A), posterior (B,) and lateral (C) based on [9]

1.2.1 Cartilage and Menisci

The articular surfaces of the art. genus are covered with hyaline cartilage, a subtype of cartilage forms in the human body that occurs primarily as articular cartilage. The hyaline cartilage serves as a sliding surface and mainly as an intra-articular "shock absorber". Its significant effect as a "shock absorber" is due to its special histological structure, which enables the so-called pressure elasticity of the tissue. Histologically, hyaline cartilage consists of chondrocytes (these make up only 5% of the volume [9]) and extracellular matrix (ECM). It is the ECM that is responsible for the mechanical function of cartilage. The ECM consists of collagen fibrils (type II, type IX, type XI), proteoglycans (PG, especially aggrecan) with glycosaminoglycans (e.g., hyaluronic acid, HA), glycoproteins (such as chondronectin as adhesion protein) and interstitial fluid (water with electrolytes and makes up about 80% of the wet weight. [10] Between the femoral and tibial joint surfaces lie two fibrocartilage discs, the so-called menisci (see Figure 2). Their main purpose is to compensate for the incongruity of the tibiofemoral joint and increase the pressure transmission surface. [5, 6]

The human knee joint comprises both a medial and lateral meniscus. The medial meniscus is crescent, increasing in width from anterior to posterior. Adhesion with the medial collateral ligament (see Ligament apparatus) and distant attachment points cause the medial meniscus to only have low mobility. This meniscus is particularly stressed during external rotation, whereas it is relaxed during internal rotation. [5, 7, 9]

In contrast to the medial meniscus, the lateral meniscus is almost circular. It is not fused to the lateral collateral ligament, which makes it more mobile and less vulnerable. [5, 7]

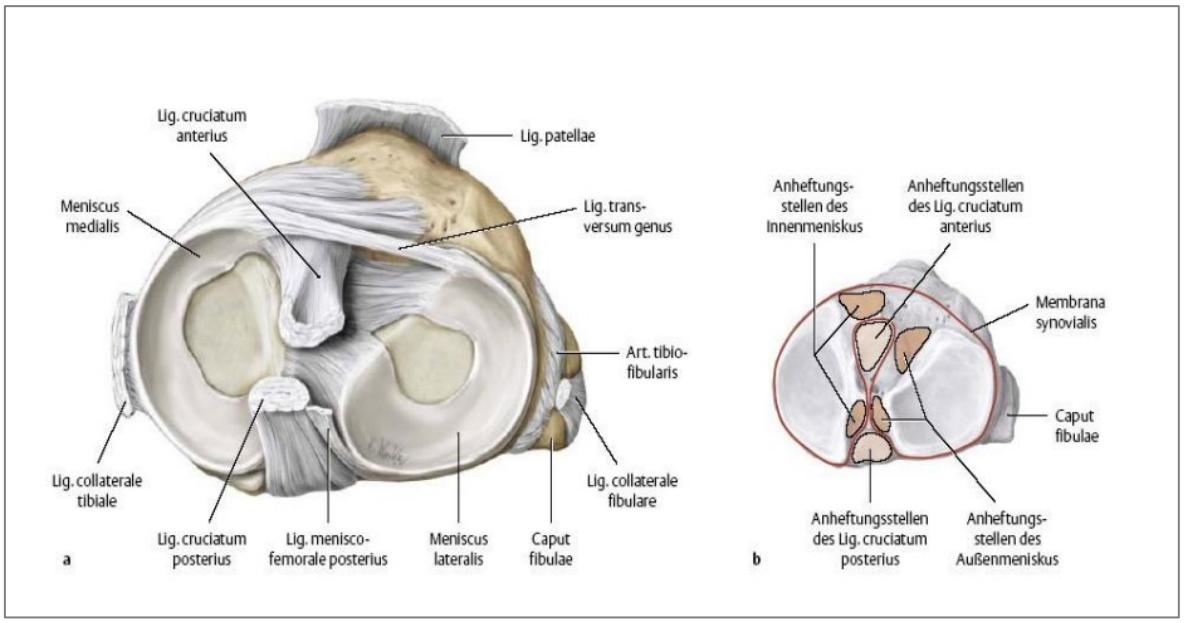

Figure 2: (a) Anatomically correct representation of the Ligaments and Menisci of the right knee at the level of the joint space in the transverse plane. (b) schematic representation with a focus on the attachment sites of the menisci and cruciate ligaments [9]

1.2.2 Ligament Apparatus

Along with the muscles, the ligamentous apparatus is mainly responsible for the stability and safety of movement in the knee joint. The ligaments are divided into external and internal ligaments, the latter running within the joint capsule. [9]

Internally, the knee is stabilized by two cruciate ligaments, both lying intracapsular but extrasynovial. [9] The anterior cruciate ligament (ACL) stretches from the lateral femoral condyle to the anterior intercondylar area of the tibia and prevents anterior translation and hyperextension. [11] The posterior cruciate ligament (PCL) stretches from the medial femoral condyle to the posterior part of the intercondylar area and prevents posterior translation and hyperflexion of the tibia. [11] Together, they also inhibit internal rotation of the tibia due to twisting around each other. [9]

Also, the menisci are strengthened by internal ligaments. The transverse ligament connects the two anterior horns of the menisci. [6] Further, the anterior (of Humphrey) and posterior (of Wrisberg) meniscofemoral ligaments originate from the posterior horn of the lateral meniscus and extend to the medial condyle of the femur, crossing the PCL anterior and posterior. [6]

The two collateral ligaments are among the most important external ligaments of the knee. The medial collateral ligament runs from the medial femoral epicondyle to the medial tibial condyle, inhibiting and protecting the knee from a valgus force. [5] The lateral collateral ligament runs from the lateral femoral epicondyle to the head of the fibula, protecting the lateral side from a varus force. [5]

The patellar ligament stretches from the patella to the tibial tuberosity. It is the attachment tendon of the quadriceps muscle and, therefore, essential for power transmission along the patella. It is surrounded by fibers from the vasti medialis and lateralis muscles, called medial and lateral retinacula. Together, they strengthen the anterior part of the capsule and stabilize the patella in its groove. [5]

On the dorsal side of the knee, the capsule is supported and reinforced by two ligaments. The oblique popliteal ligament stretches from the tendon of the semimanbranosus muscle to the lateral condyle of the femur, and the arcuate popliteal ligament originates of the head of the fibula, crosses the tendon of the popliteal muscle and inserts on the lateral condyle of the femur. [5]

1.3 Gonarthrosis Deformans

Gonarthrosis, also known as knee osteoarthritis, is a chronic and progressive degenerative condition characterized by the gradual deterioration of the articular cartilage within the knee joint. This degenerative process extends beyond the cartilage and affects the surrounding structures, including the peri- and intra-articular ligaments, muscles, synovial membrane, and fibrous joint capsule. This condition progressively impairs joint function, leading to pain, stiffness, decreased range of motion, and reduced quality of life for individuals affected. [12, 13]

1.3.1 Epidemiology

Various sources provide consistent data on the prevalence of gonarthrosis. For instance, the prevalence of radiographic signs of gonarthrosis is approximately 15-16% among individuals aged 50-54 years and as high as 34-40% among those aged 70-74. [14] Moreover, around 24% of individuals over the age of 60 exhibit

both radiological and clinical indications of gonarthrosis. [14] It is important to consider a study involving a substantial sample size of 6,800 participants, which revealed a significant disparity between radiographic knee OA, knee pain, and the diagnosis of arthritis by physicians. [15]

In another comprehensive study focusing on symptomatic OA, incidence rates were observed to increase age-related. Among women aged 70-89, the incidence of knee OA approached 1% per year. [16]

1.3.2 Etiology

Gonarthrosis is divided into primary and secondary osteoarthritis. In primary OA, no clear cause for the development can be ascertained from the patient's medical history. The predisposing factors are mainly old age, female sex, and a body mass index (BMI) above 25. [17]

In secondary osteoarthritis, there are known causes for the development. It is further subdivided into post-traumatic osteoarthritis (e.g., after fracture with joint involvement, chronic instability after ligament or meniscus lesion, traumatic cartilage lesion), congenital and acquired osteoarthritis (e.g., epiphyseal dysplasia, axial deviations, chronic joint damage due to overuse), metabolic and endocrine osteoarthritis (e.g., hemochromatosis, diabetes mellitus, hypercholesterolemia, hyperuricemia), inflammatory osteoarthritis (e.g., rheumatoid arthritis, bacterial arthritis), and osteoarthritis of other causes (e.g., avascular bone necrosis, neuropathic arthropathies). [17]

1.3.3 Pathophysiology

To maintain its typical compressive-elastic properties against mechanical stress, articular cartilage must continuously renew itself. This renewal occurs through a balance of anabolic and catabolic cartilage remodelling processes. In the osteoarthritic knee joint, dysbalance favours the catabolic metabolism. [18] Interleukin 1 (IL-1) and tumor necrosis factor-α (TNF-α) seem to play a decisive role. On the one hand, these two factors cause a decreased synthesis of collagen

and proteoglycans. On the other hand, chondrocytes and cells of the synovial membrane are stimulated to produce proteolytic enzymes such as collagenases and gelatinases, which damage the cartilage. On the other side of the scale are anabolic factors like insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), and transforming growth factor β (TGF-β), which stimulate cell metabolism and antagonize inflammatory mediators. The concentration of anabolic growth factors decreases throughout life, further favouring osteoarthritis in old age. If a dysbalance now occurs, the structural damage begins first with the breakdown of collagen II on the cartilage surface. In response, chondrocytes synthesize more atypical matrix components, and additional dedifferentiation of the cartilage cells occurs. [18]

1.3.4 Classification

The classification of arthrosis into degrees of severity is primarily based on X-ray diagnostics, as it is currently still considered as gold standard for the diagnosis. [19] Computed tomography, conversely, plays a subordinate role in classifying gonarthrosis. The first classification of osteoarthritis into degrees of severity was made by Kellgren and Lawrence in 1957 (see Figure 3 and Table 1). [20] To date, other classifications like Ahlbäck, ICRS (International cartilage repair society), and Jäger-Wirth have emerged. Therefore, it should always be stated according to the osteoarthritis classification. [19]

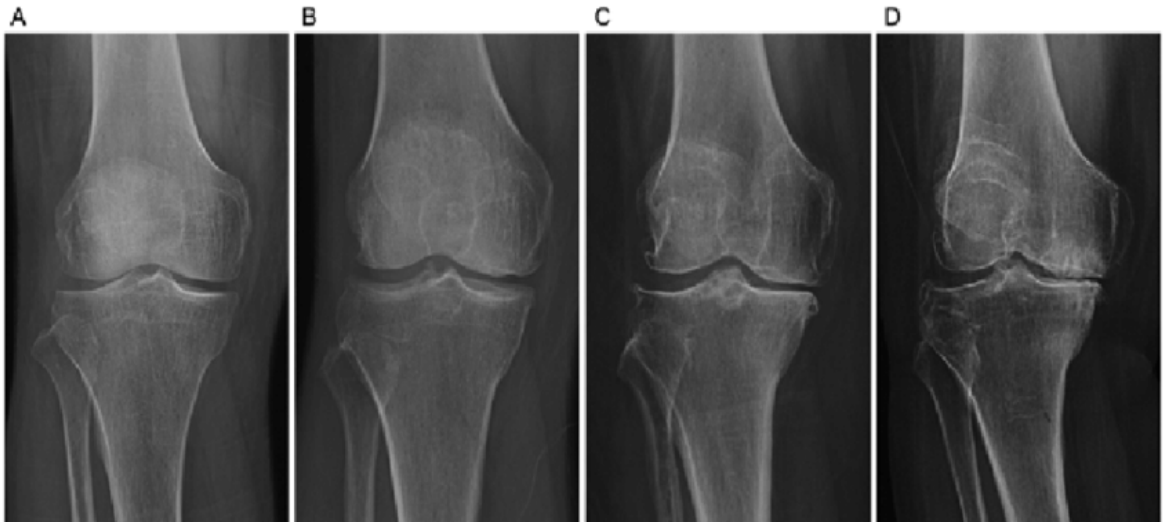

Figure 3: Radiological classification of OA after Kellgren and Lawrence from (A) Grade 1 to (D) Grade 4. [21]

Grade	Grade 1	Grade 2	Grade 3	Grade 4
Kellgren and Lawrence [20]	doubtful joint space narrowing and possible osteophytic lipping	definite osteophytes and possible joint space narrowing	moderate multiple osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bone ends	large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends

Table 1: Classification of OA after Kellgren and Lawrence

OA can be further divided into three forms after its location. The unicompartmental form involves either the patellofemoral, medial tibiofemoral, or lateral tibiofemoral compartment. In the bicompartmental form, there is bilateral tibiofemoral damage, and when all three compartments are affected, it is defined as pangonarthrosis. [19]

1.4 Treatment

The therapy of gonarthrosis is based on several pillars. Since a cure in the restoration of the original cartilage biology cannot be achieved, symptomatic treatment plays a key role. In addition to symptom control, the course of the disease must be slowed down or, at best, interrupted. [22]

The optimal form of therapy is influenced not only by the duration and severity of the disease but also by the affected person`s age, state of health, and personal expectations. At the beginning of treatment, conservative therapy is usually the main option. [22] Only after conservative measures have been exhausted, surgery is indicated, if necessary. [22] Due to individual needs and many therapeutic options, there is no valid algorithm for all patients. The Association of the Scientific Medical Society (AWMF) has attempted to provide an overview of the treatment options in its guideline "Gonarthrosis", excerpts of which are presented below. [14]

In consensus between patients and physicians, a suitable form of therapy should be found for the individual patient. The prerequisite is informing patients about the disease and the possibilities for influencing its course. [14]

Regular exercise is important for optimal joint nutrition and maintaining adequate mobility. In addition to improvements in knee-related quality of life, exercise therapy often also improves psychosocial factors and should therefore always be recommended if possible. [23] Another therapeutic goal is to reduce excess weight, which is often very difficult due to the pain associated with physical activity. [22, 23]

Physical therapy is another very important pillar in the therapy of gonarthrosis.
Further measures include extracorporeal shock wave therapy (ESWT), transcutaneous electrical nerve stimulation (TENS), laser therapy, electrophysical therapies, traction treatment, occupational therapy, and naturopathic therapies such as acupuncture, hydrotherapy, and balneology. In addition, orthopedic procedures such as shoe adjustments with outer or inner rim elevation, ankle joint orthoses, gonarthrosis orthoses, and knee bandages can be used for special problems. [14]

1.4.1 Drug Therapy

The working group of the scientific medical societies (AWMF) has identified a range of drug therapy options for gonarthrosis, including topical or oral non-steroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids, hyaluronic acid, and glucosamine. [14]

Non-steroidal anti-inflammatory Drugs

NSAIDs are pharmacological agents that exert analgesic, anti-inflammatory, and antipyretic effects by inhibiting the cyclooxygenase enzymes involved in the synthesis of prostaglandins, thereby modulating the inflammatory response. [24]

The use of NSAIDs can reduce this pain and thus reduce the need for other analgesics. In addition to their analgesic effect, NSAIDs also have an antiphlogistic effect, which is a desirable and therapeutic aspect, especially in inflammatory arthritis pain. Topical application of NSAIDs is less likely to cause gastrointestinal side effects than oral, which is why the topical application is preferable, especially

in older age. The adverse effects of topical application are mainly local redness and itching. [14]

If the analgesic effect of topical application is insufficient, oral administration of NSAIDs should be considered. However, oral NSAIDs are not suitable as permanent medication. Their use is limited to periods of pain and inflammation. The dose should be kept as low as possible. Especially in elderly patients, oral NSAIDs should be used with caution. [14]

With oral application, gastrointestinal and cardiovascular risks are paramount and may contraindicate use. In case of increased gastrointestinal risk, additional administration of proton pump inhibitors is indicated. [14]

Corticosteroids

Corticosteroids are a class of steroid hormones that mimic the effects of cortisol, exerting potent anti-inflammatory, immunosuppressive, and metabolic actions mainly through suppression of multiple inflammatory genes and their interaction with specific cellular receptors. [25, 26]

Intra-articular injection of corticosteroids provides potent local anti-inflammation and pain relief for up to four weeks. For this purpose, the smallest effective dose should be used, since larger amounts of corticosteroids can negatively affect cartilage cell metabolism. Due to the risk of septic arthritis, the application should be strictly aseptic and thus requires some experience in intra-articular application or infiltration. [14]

Hyaluronic Acid

Hyaluronic acid, administered via intra-articular injection, exhibits therapeutic efficacy in osteoarthritis by improving joint lubrication, reducing inflammation, modulating cartilage metabolism, and providing chondroprotective effects through its viscoelastic and immunomodulatory properties. [27] For several decades, hyaluronic acid has been used as an agent in the symptomatic treatment of osteoarthritis, although controversy exists in the literature regarding its efficacy. [14] Reviews from 2015 and 2012 questioned the clinical efficacy of this treatment

modality. [28, 29] In contrast, more recent studies suggest a clinically relevant analgesic effect. [30, 31] Compared to intra-articular injection of corticosteroids, a meta-analysis from 2017 showed a worse short-term effect (effect within four weeks after application) of hyaluronic acid in terms of pain relief. However, hyaluronic acid showed a better long-term effect (up to a period of 6 months). [32]

Especially in the presence of contraindications to the use of NSAIDs or when they have shown an insufficient effect, intra-articular hyaluronic acid injection can be considered. [14] However, further clinical studies are required to define a patient population that benefits most from intra-articular injection with hyaluronic acid. [32]

Glucosamine

Glucosamine is a natural amino sugar that has been shown to exhibit efficacy in osteoarthritis therapy by promoting cartilage synthesis, inhibiting cartilage degradation, and reducing pain and inflammation through its involvement in glycosaminoglycan production and modulation of inflammatory pathways. [33]

In the presence of NSAID intolerance, systemic administration of glucosamine may be attempted for symptomatic treatment of osteoarthritis. However, the symptom-relieving effect of these preparations is controversial in the literature. Also, a widely proposed chondroprotective effect of glucosamines has not yet been proven. [14]

Opioids

Opioids encompass a diverse range of chemical compounds, including natural, synthetic, and semisynthetic substances, all of which exert their effects by binding to opioid receptors in the central nervous system and peripheral tissues and further inhibit the transmission of pain signalling. [34]

Compared with NSAIDs, opioids show comparable efficacy with better gastrointestinal tolerability. However, this is offset by opioid side effects such as a tendency to fall, dizziness, and impaired balance. Furthermore, an increased preoperative need for opioids poses an increased risk for chronically increased or

prolonged postoperative opioid use. Therefore, weak opioids should be used at the lowest effective dose. [14]

1.4.2 Knee Arthroplasty

Surgical treatment options include joint-preserving procedures (such as arthroscopic meniscus therapy), cartilage replacement procedures, osteotomies, and joint-replacing procedures (Knee Arthroplasty). (20) Since the study is based on the outcome of the latter option, joint-replacing procedures are discussed in more detail in the following chapter.

Knee arthroplasty is a surgical procedure that involves the removal of damaged articular surfaces of the knee joint and subsequent the replacement with prosthetic components to alleviate pain, restore joint function, and improve the quality of life for patients with severe knee pathology like OA. Its appropriateness and success depend on various factors such as patient characteristics, stage of disease, previous treatments, comorbidities, and possibly also the experience and capabilities of the surgeon. Therefore, a set of criteria must be considered when determining the indication. [35, 36]

Absolute indications are knee pain for at least 3–6 months, evidence of structural damage (osteoarthritis, osteonecrosis), failure of conservative therapy measures for at least 3–6 months, and subjective suffering and a reduction in quality of life. [35]

Relative indications are reduced walking distance, pain when standing for long periods or climbing stairs, limited ability to cope with everyday life, malalignment of the leg axis, instability of the knee joint, and functional limitations of the knee joint or leg (strength, mobility). [35]

Absolute contraindications are infection in the knee joint and general contraindications for elective surgery (e.g., an acute cardiovascular event). [35]

Relative contraindications are very high BMI (> 40), significantly shortened life expectancy due to comorbidities, substance dependence, and psychiatric concomitant diseases. [35]

Types of Knee Arthroplasty

Various types of knee prostheses are available for knee arthroplasty, each tailored to the specific local conditions, including ligament stability and affected joint compartments. A brief description of each type is provided below.

Unicompartmental Knee Arthroplasty (UKA)

In UKA, only one compartment of the joint components is replaced (see Figure 4). Therefore, areas of application for this type of prosthesis are isolated arthrosis of the patellofemoral, medial or lateral compartment, mainly due to axial misalignment. [37, 38]

Bicompartmental- (BKA) and tricompartmental/total Knee Arthroplasty (TKA)

In the case of bicompartmental and tricompartmental knee endoprostheses, also known as total knee endoprostheses, two or three compartments are replaced with artificial joint components. The most common method is the replacement of the medial and lateral compartments (bicompartmental endoprosthesis) (see Figure 4). Additional to these two compartments, a posterior patellar replacement (tricompartmental endoprosthesis) can be performed, but indications are still discussed controversially in the literature. [37]

In the case of TKA, systems with fixed and mobile bearings (with polyethylene inlays) can be distinguished. Prosthesis with mobile bearing should improve the sliding partners´ conformity with good mobility and low polyethylene stress. However, no significant difference between the two types could be shown in either function or survival rate in long-term studies. [39]

In bi- and tricompartmental knee endoprostheses, joint guidance is ensured by the capsule-ligament apparatus. For this reason, an intact ligamentous apparatus is a mandatory prerequisite for these types of prostheses. There are further variations regarding the preservation of the cruciate ligaments. While the anterior cruciate ligament is removed in most cases, there are two options for the posterior cruciate ligament. It can either be preserved (cruciate ligament-preserving knee endoprostheses), or removed, resulting in a cruciate ligament-replacing knee

prosthesis (posterior stabilized). Both variants have advantages and disadvantages, which must be weighed up according to individual criteria. [37]

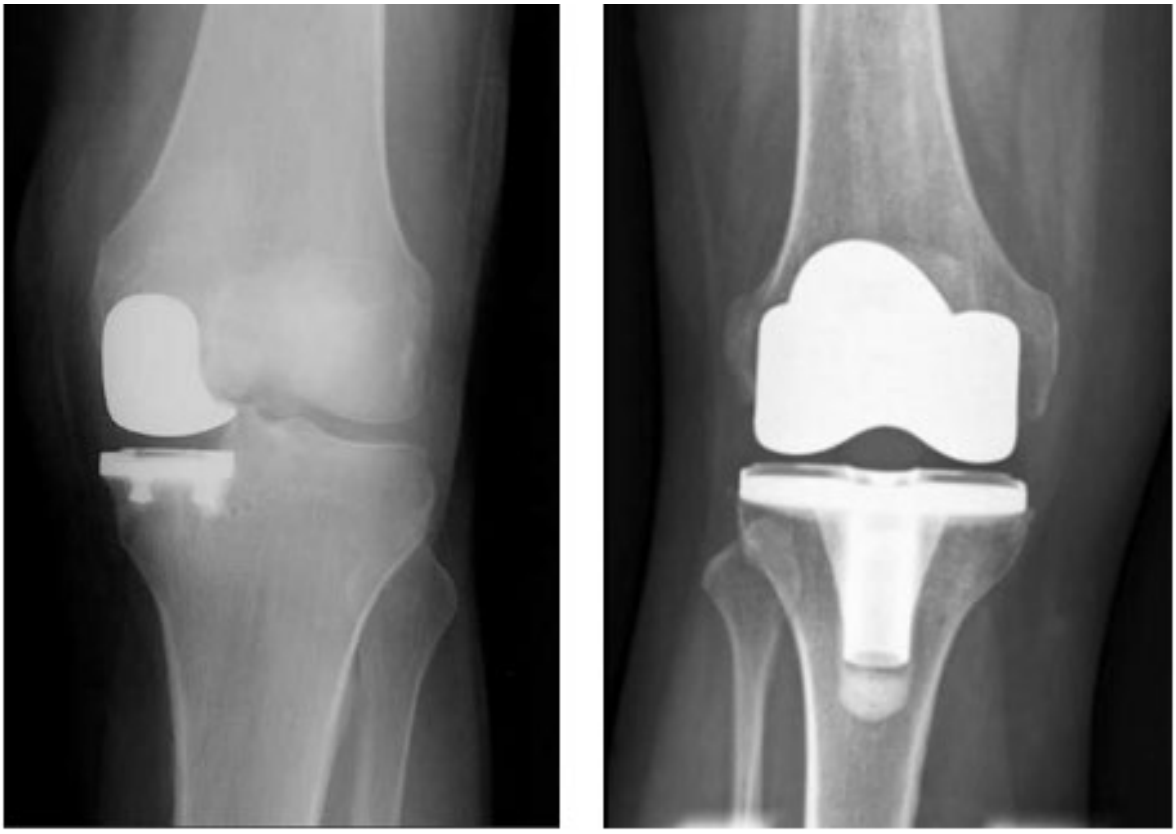

Figure 4: UKA of the medial compartment on a left knee (left), TKA of the right knee (right) [Department of Orthopaedics and Traumatology of the Medical University of Graz]

Anchoring

Anchoring in total knee arthroplasty refers to the secure fixation of prosthetic components to the bone using various techniques, such as cement, screws, or press-fit. Cemented anchoring is the gold standard nowadays, showing a fully loadable primary stability and a better distribution of pressure at the femoral oblique incisions while also allowing infection prophylaxis through the addition of antibiotics in comparison to cementless anchorage. [37]

Complications

Since knee arthroplasty is a major surgery that requires a profound knowledge of the anatomy and biomechanics of the knee joint, as well as extensive surgical skills, a variety of complications, are possible. Referring to an analysis including

391,913 cases of primary and 36,307 (9%) cases of revised TKA, the most common causes for revision surgery in TKA in relative terms are aseptic loosening (29.8%), septic loosening (14.8%), pain without other reason (9.5%), wear (8.3%), instability (6.2%), implant breakage (4.7%), periprosthetic fracture (3%). [40]

1.5 Pain

The International Association for the Study of Pain (IASP) defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” in 1979, and since then it has been established as such in scientific circles. [41]

But since this explanation encompasses various important concepts, it must be explained further. Pain is a subjective experience and therefore needs consciousness to be measured. Pain can also be described as an “experience” to separate it from “nociception”, which is the neural process including the transduction and transmission of noxious stimuli to the brain via a so-called pain pathway. Pain occurrence results from an interplay between signalling systems, modulation from higher brain areas, and the unique perception of each individual. [42]

From an evolutionary standpoint, the development of pain served a protective role by acting as a warning system for harmful stimuli. However, in contrast to inflammatory pain, evolution has failed to adapt to our expanded ability to survive trauma, diseases, and iatrogenic trauma such as surgery. In these interrelationships, pain is no longer a helpful function but becomes a disease on its own. [43] Conceptualizing pain as a homogeneous entity might be easy, but it is an oversimplification of several complex neurobiological and pathophysiological interactions.

1.5.1 Classification of Pain

Pain is often classified based on its duration or underlying cause. When considering duration, pain is categorized as either acute or chronic. The specific

timeframe to distinguish between acute and chronic pain varies, with commonly used thresholds ranging from three to six months after the onset of pain, although some researchers may utilize a 12-month cut-off. [44]

Considering the cause, pain can be divided into three types: nociceptive pain, nociplastic pain, and neuropathic pain. All three types may present clinically similar, but their underlying causes are different and therefore they cannot be adequately treated in the same way. In the following section, all types are briefly discussed, but since this study focuses on the recognition and treatment of neuropathic pain, this subtype will be considered in greater detail within the context of this paper.

Nociceptive pain

Specialized peripheral sensory neurons called nociceptors detect extremes in pressure, temperature, and injury-related chemicals, transducing these stimuli into electrical signals and relaying them to higher brain centers to alert the body to potentially damaging stimuli. [45] Nociceptors are present in almost all tissues but exhibit their highest density in the skin. Exceptions to their occurrence include the brain and the parenchyma of organs. Pain nociceptors can be subdivided into monomodal receptors (mechanoreceptors/thermoreceptors) and polymodal receptors.

Mechanoreceptors open to a mechanical deformation, leading to an influx of cations such as Na+, K+, and Ca2+ into the nerve fiber. In most cases, they also have transient receptor potential channels (TRPV), which can be activated by noxious heat (above around 42 degrees Celsius) or chemically, e.g., by capsaicin or an increased proton concentration during acidosis (see Figure 5). [46]

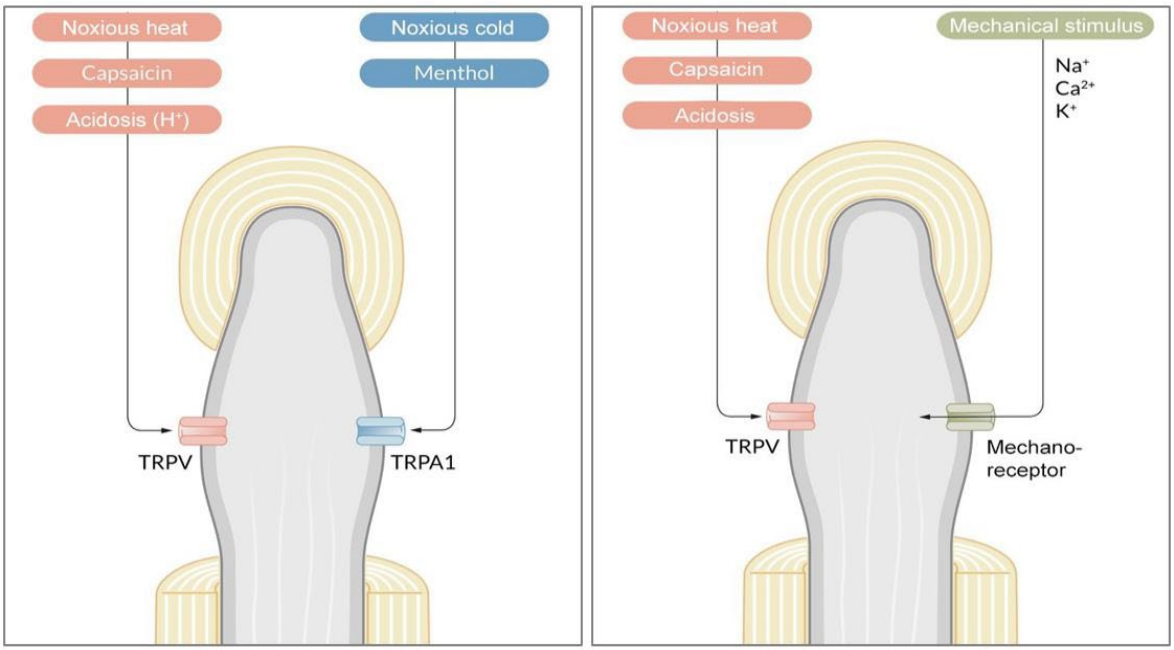

Figure 5: Schematic thermosensitive nociceptor with channels and corresponding stimuli (left) and schematic thermosensitive nociceptor with channels and corresponding stimuli (right) based on [46]

Thermosensitive nociceptors possess TRPVs for detecting noxious heat stimuli, and transient receptor potential ankyrin 1 (TRPA1) channels that can be activated by cold stimuli below five degrees celsius or chemically by the molecule menthol (see figure 5). [46]

In addition to mechanical and thermal (above 42 or below 15 degrees Celsius) stimuli, polymodal nociceptors primarily respond to chemical stimuli mediated by a variety of specific receptors, the most prominent of them are shown in Figure 6. [46]

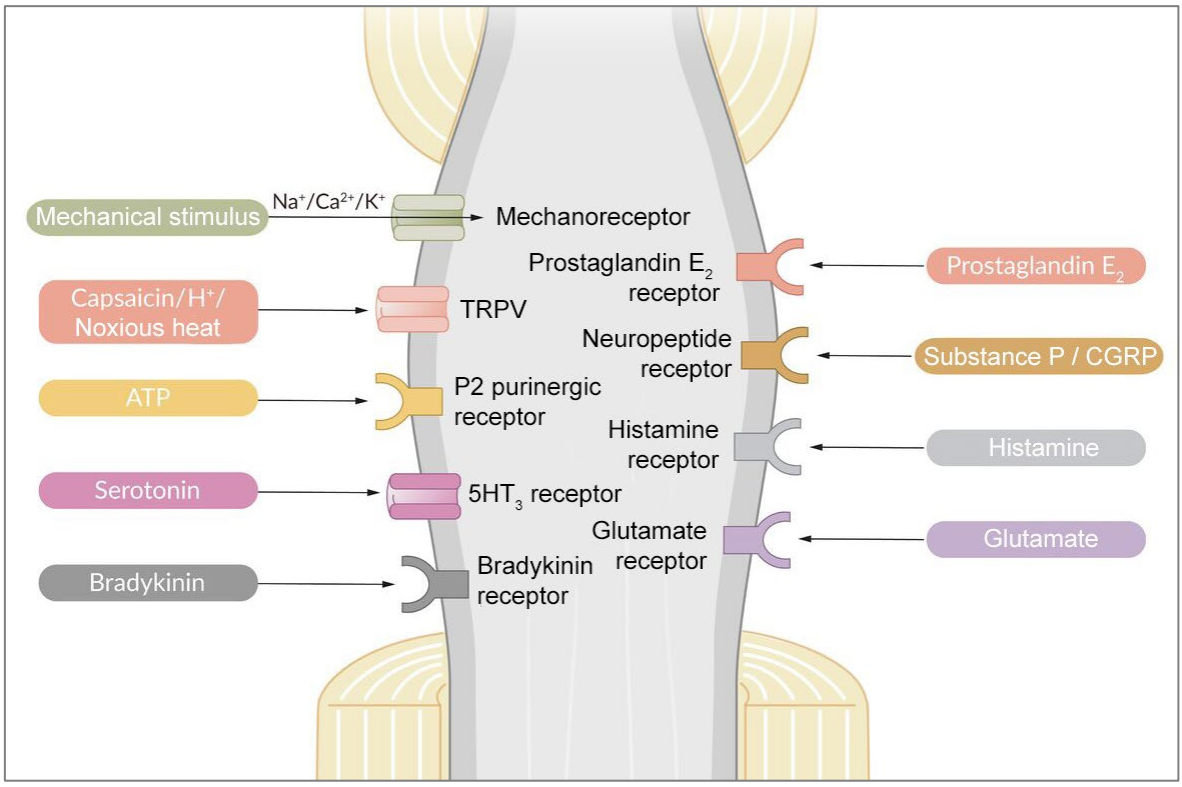

Figure 6: Polymodal nociceptor with channels and corresponding stimuli based on [46]

Monomodal and polymodal receptors additionally differ in their stimulus transmission. The afferents of monomodal receptors consist of fast conducting Ad-fibers (approx. 15m/s) and thus lead to a fast, well localizable pain when excited. Afferents of polymodal nociceptors consist of slowly conducting C-fibers (approx. 1m/s) and lead to delayed, poorly localizable pain. [46]

Ascending Nociceptive Pathways

The ascending nociceptive pathways are responsible for pain sensation and, like all other somatosensory pathways, have three neurons. In addition, there may be many modulating interneurons, but these are not counted individually. Pain transmission from the head region differs in its wiring at the brainstem level from the transmission of the rest of the body. [46]

The posterior cord pathways (fasciculus gracilis and fasciculus cuneatus) are responsible for the transmission of tactile sensations of all mechanosensors and conscious proprioception. While the fasciculus gracilis mainly transmits information of the lower half of the body, the fasciculus cuneatus mainly transmits information

of the upper half of the body. Fibers of the first neuron enter the spinal cord via the posterior root without switching at first. It leads upwards in the posterior cord until switching to the second neuron in the Ncl. Cuneatus/Gracilis as well as crossing to the opposite side (decussation lemniscorum). Afterward, it leads through the mesencephalon to the thalamus, where it switches to the third neuron and proceeds forward to the somatosensory cortex (see Figure 7). [46]

The anterior cord (tractus spinothalamicus anterior and lateralis) is responsible for the transmission of pain, temperature, and gross pressure sensations. Fibers of the first neuron also enter the spinal cord via the posterior root, although the tractus spinothalamicus anterior may also enter one to two segments higher or lower. Switching to the second neuron happens immediately in the posterior horn, followed by segmental crossing in the commissura alba anteriorly. Fibers lead upwards to the thalamus as the anterior cord, there switching to the third neuron and forwarding to the somatosensory cortex (see Figure 7). [46]

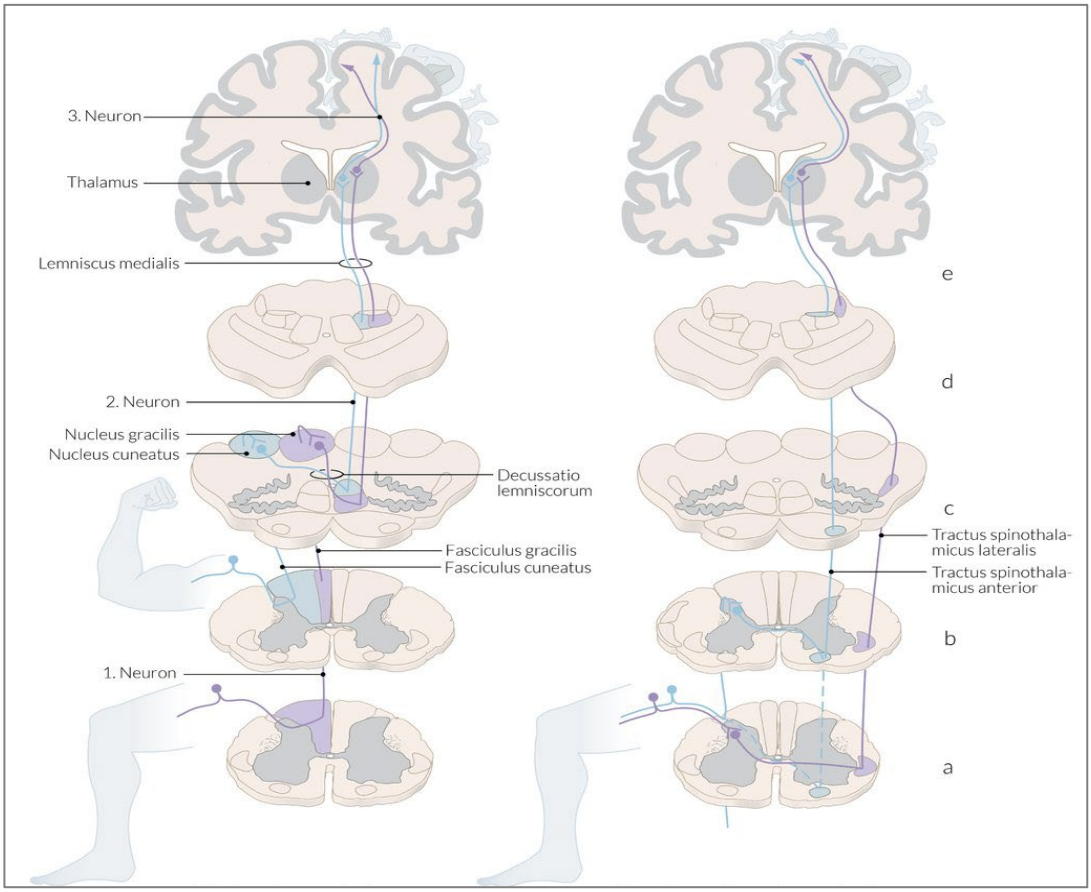

Figure 7: Nociceptive Pathways of the posterior (left) and anterior (right) cord pathways based on [46]

Nociplastic Pain

The mechanisms underlying nociplastic pain are not entirely understood yet, but it is thought that augmented pain and sensory processing in the CNS and altered pain modulation are key factors in its development. Observed symptoms in nociplastic pain include a more widespread and/or intense pain than it would be expected regarding the identifiable nerve or tissue damage, as well as other CNS-derived symptoms like fatigue, memory-, sleep-, and mood problems. It can occur isolated in conditions such as tension-type headache and fibromyalgia, or in mixed pain states with ongoing neuropathic or nociceptive pain, for example in chronic low back pain. [47]

Neuropathic Pain

Neuropathic pain is caused by a disease or lesion of the somatosensory nervous system and is a common condition in chronic pain, with major impact on the quality of life. There are various causes for the development including polyneuropathy, trigeminal neuralgia, central poststroke pain, postherpetic neuralgia, and postsurgical pain. Most patients suffering from neuropathic pain complain of intermittent or ongoing spontaneous pain. Although neuropathic pain can imponate in any way, it is typically described as either burning, pricking, shooting, pinprick-like, freezing, or squeezing pain. [48] This spontaneous pain sometimes is dominated by electric shock-like pain paroxysms, either in addition to the ongoing pain or alone. There also may be sensations, including paraesthesia, which are abnormal, but not unpleasant sensations, and dysesthesia, which are abnormal and unpleasant sensations. [49] They both may occur evoked or spontaneously. Evoked pain can rarely manifest on its own without any spontaneous pain, but rather occurs in addition to it, while spontaneous pain on the other side frequently occurs without evoked pain. This suggests that the mechanisms behind them are overlapping but not the same. [50]

There is strong evidence, that early hypersensitivity or evoked pain in postherpetic neuralgia, postsurgical pain, and central poststroke pain predicts the subsequent development of neuropathic pain. [51–53]

To better understand the pathophysiology behind the development of neuropathic pain, the latest research done in the field will be discussed briefly in the following chapters.

Peripheral Sensitization

If tissue gets injured, several inflammatory and reparatory processes ensue, which lead to a hyperexcitable state of the tissue surrounding the injury, known as peripheral sensitization. [43] Different factors contribute to this phenomenon. Nociceptive terminals release inflammatory mediators like substance P and calcitonin gene–related peptide, leading to increased vascular permeability and therefore to localized edema. By-products such as cytokines, prostaglandins, bradykinin, and growth factors can sensitize and excite nociceptors, resulting in ectopic discharges and lowered firing thresholds. [43]

Ectopic discharges are spontaneously occurring electrical impulses that originate either from the dorsal root ganglion, along the injured nerve, or from uninjured adjacent fibers due to ephaptic transmission. In such a state, 15–50% of the patients can suffer from dysesthesia, like allodynia and hyperalgesia (see Figure 8). [54] Allodynia is a condition where the pain is caused by a normally non-painful stimulus. Hyperalgesia refers to an exaggerated pain perception in response to a painful stimulus. It can further be categorized into primary and secondary hyperalgesia, with primary occurring directly in damaged tissue and secondary occurring in the surrounding undamaged tissue. [54]

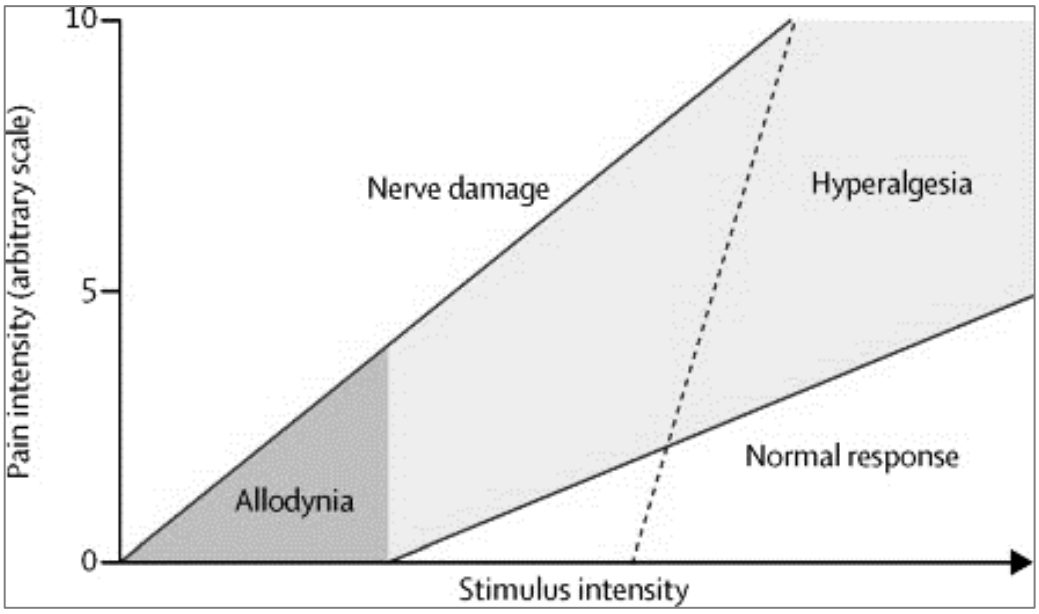

Figure 8: Differences in Pain intensity of normal response, Allodynia, and Hyperalgesia due to stimulus intensity, based on Figure 1 in [54]

Alterations in Ion Channels

The first point of contact between noxious stimuli and activation of pain pathways is made at peripheral nociceptive endings. For this interaction to take place, mechanical, chemical, and physical stimuli must be transduced into membrane potential differences and, furthermore, trigger action potentials if a particular threshold is reached. Several ion channels, such as acid-sensing ion channels (ASIC), ATP-gated purinergic channels (P2X), and several channels of the transient receptor potential channel (TRP) family are involved in this process (see Figure 5). Subsequently, TRP are amplified by voltage-gated sodium channels and those reaching depolarization levels then trigger action potentials. Several types of potassium channels are able to block transient potentials by hyperpolarization and calcium channels at nerve endings regulate neurotransmitter release by facilitating SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complex-mediated vesicle fusion. These ion channels are under strict regulatory control by posttranslational modifications and at the transcriptional level, which may be deregulated upon nerve injury. [55]

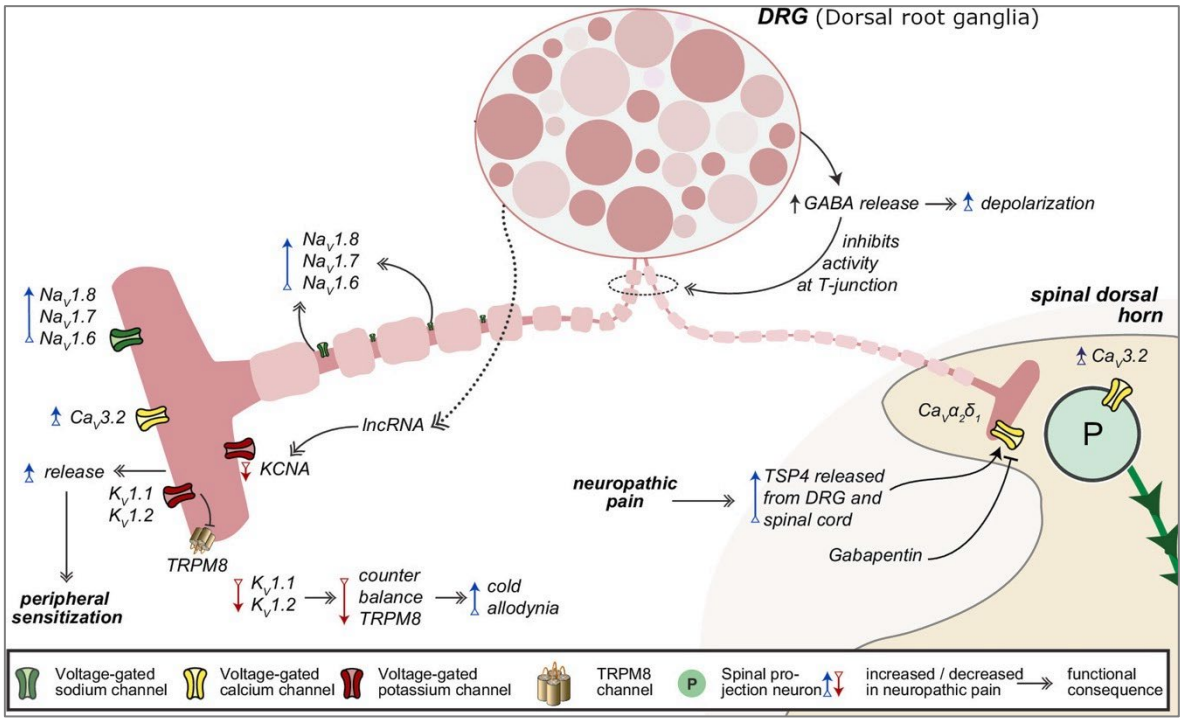

Figure 9: Ion-channel dysregulation in sensory spinal circuits within neuropathic pain based on Figure 5 in [55]. The upregulation of pro-excitatory ion channels enhances excitability, ectopic firing, and neurotransmitter release of peripheral sensory neurons.

At least eight channels of the TRP family (TRPV1, TRPV2, TRPV3, TRPV4, TRPA1, TRPM2, TRPM3, and TRPM8) are known to be expressed in peripheral sensory neurons and therefore implicated in several aspects of thermal encoding and nociceptive transduction. Although no major associations between mutations in TRP channels and neuropathic pain syndromes have been found in human genetic studies, rodent models show that a blockade of some TRP channels alleviates neuropathic hypersensitivity. [56]

Voltage-gated sodium channels are the main molecular moiety for propagating the axonal action potential and therefore play a significant role in handing off information from pain receptors in the peripheral nervous system (PNS) to the central nervous system (CNS). Furthermore, there is evidence that they are also involved in the transduction of a painful stimulus into an electrical impulse in nociceptive receptors themselves. [57, 58]

Recombinant DNA studies have shown that rather than being expressed by a single gene, sodium channel polypeptides in most organisms exist as multigene families, where the individual gene products of those are called isoforms.

Currently, there are known to be at least nine distinct types of sodium channels in mammals. [59]

With the use of immunocytochemical approaches, it has been seen that among the known isoforms, $Na_V1.1$, $Na_V1.6$, $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$ are selectively expressed in pain-conducting pathways of the peripheral nervous system. [59]

There is also compelling clinical evidence for the involvement of peripheral nervous system isoforms in pain due to studies of human familial pain disorders. Particularly gain of function mutations in the NaV1.7 isoform, leading channels to either open more frequently to depolarizing stimuli or being less affected by the inactivation of resting membrane potentials. Either way, nociceptor cell bodies, axons and/or free nerve endings are getting active to stimuli below their normal threshold or even spontaneously, leading to dysesthesia in the patient. [59, 60]

Another family of excitatory channels linked to neuropathic pain are hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels. Rodent neuropathic pain models show evidence of increased expression of HCN1 and HCN2 in the spinal cord, some brain regions, and sensory neurons. [61]

Voltage-gated calcium channels regulate neurotransmission and cellular excitability at several avenues in somatosensory nociceptive pathways. Due to their importance to neuronal activation and rhythmicity, they are constituted as highly druggable targets in several neural disorders, including chronic pain. [55] Ziconotide, ethosuximide, and gabapentin are already used in pain management, but due to their cardiovascular and neurological side effects, their efficiency must be rationalized. To optimize results, their precise signalling mechanism must be understood and further, more specific subtype blockers need to be developed. [55]

Along the subtypes, CaV3.2 is in the center of focus. It is increasingly expressed in models of traumatic nerve injury, like the spared nerve injury model (SNI), and chemotherapy-induced neuropathy. CaV3.2 inhibitors showed a preventing but no reversing effect on placitaxel induced neuropathic allodynia and spontaneous activity in neurons, suggesting indications for their use in the early phase of establishing neuropathic pain. [62]

Also, $Ca_v\ \alpha_2\ \delta_1$, a target of gabapentin, is staying under research focus with new perspectives for its interactions with thrombospondins that lead to participation in synaptogenesis being made, albeit it has low estimated efficacy. [63]

Alterations in neuropathic pain-related ion channels are not only restricted to pronociceptive ion channels but extend to diverse ion channels which diminish neuronal excitability. Considerable new developments in the understanding of potassium channel function regulation in sensory spinal circuits in neuropathic pain have been made. [55]

Furthermore, there are new insights into shaker-like potassium channels (KV1.1 and KV1.2) and their selective modulation in cold-induced allodynia. A recent study also reported an increase of cold-sensitive neurons (CSNs) in dorsal root ganglia contributing to the sciatic nerve, leading to a decreased cold temperature threshold in patients with cold allodynia evoked by nerve injury. [64]

GABA channels are not only responsible for shaping pre- and postsynaptic inhibition of central circuits but have also been found to be regulators of dorsal root ganglia excitability. A recent study demonstrated that GABA infusion into the dorsal root ganglia leads to repressed excitability of sensory neuron somata and reduced neuropathic hypersensitivity, while the use of antagonists increased nociception-induced excitation, suggesting that GABAergic channels and also classes of potassium channels deliver hope for novel analgesics. [65]

Immune Cells

There is already knowledge about the contributions to pain of several types of immune cells including neutrophils, mast cells, T-lymphocytes, and macrophages, both in central and peripheral sensitization (see Figure 12). Among the most prominent immune cell-derived factors are tumor necrosis factor alpha (TNF-α), interferon-y, and several interleukins (IL-10, IL-4, IL-17, IL-1β). [55]

Initially thought to be relevant mostly to inflammatory pain disorders, there is now plenty of evidence that also neuropathic pain states are associated with increased infiltration of several types of immune cells, with T-cells being an especially interesting research topic currently. Studies made in 2016 have shown that mice

lacking T-cells are not able to develop mechanical allodynia after nerve injury due to the loss of leukocyte elastase, which normally has pronociceptive effects in peripheral sensory neurons. [66]

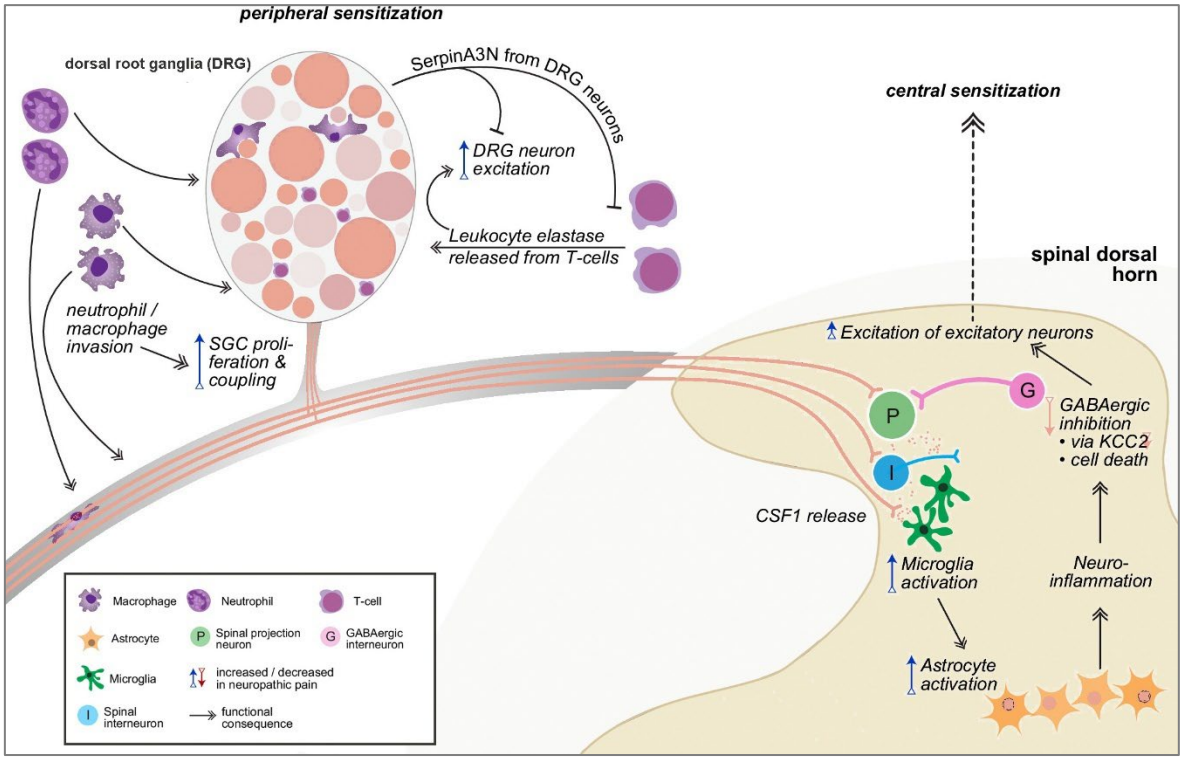

Figure 10: Interaction and temporal sequelae of neuroinflammatory processes in neuropathic pain based on Figure 6 in [55]. Invading macrophages, neutrophils and T cells lead to peripheral and central sensitization by releasing mediators like interleukins, TNF-α, and leukocyte elastase.

It has also been shown that natural killer cells are involved in the development of neuropathy through an upregulated ligand in the dorsal root ganglia neurons, activating and mediating them to invade injured neurons, leading to their degeneration. [67]

Macrophages are involved in promoting sensitization through M1-type, and both inhibiting healing and promoting sensitization through M2-type macrophages with mounting evidence. [68, 69] This leads to an enormous potential for target therapy against immune cells and their mediators in patients with neuropathic pain.

Metabolites, mitochondrial factors, and Hypoxia

Mitochondrial dysfunction of peripheral sensory neurons is another driving factor in neuropathic pain. It can be induced by direct nerve injury, chemotherapeutics, and

other immunosuppressive therapies, as well as high levels of glucose and its metabolites. [70] Due to their high energy demands, peripheral sensory neurons are especially vulnerable to bioenergetic crises in injuries, leading to an increased generation of reactive oxygen species (ROS) and further their degeneration. [55]

There are also studies suggesting that the harmful effects of ROS and mitochondrial dysfunction lead to increased superoxide levels in the dorsal horn of the spinal cord. These further lead to an increased frequency of postsynaptic currents from excitatory neurons in the spinal cord. Therefore, overexpression of antioxidant enzymes like superoxide dismutase-2 leads to protection against nerve injury-induced neuropathic allodynia. [71, 72]

Glial-derived Mediators in peripheral Nerves and Spinal Cord

In the past years, both central and peripheral glia have been under focus in neuropathic pain research. Following an injury, the increased pathological activity in peripheral afferent neurons leads to the release of colony stimulating factor 1 (CSF1) in central terminals of those afferents. [73] Together with ATP, this leads to proliferation, activation, and shape change of microglial populations inside the dorsal horn of the spinal cord. Changes in the secretory and transcriptional profile of the microglia, including the release of diverse interleukins, TNF, fractalkine, chemokines, ATP, and others follow. The triggered neuroinflammatory cascade then further propagate through the recruitment of neighbouring astrocytes and other microglia, which themselves release pro-inflammatory enzymes as well. [66]

In peripheral glia, satellite glia has gained most attention in research due to its important role in forming gap junctions and showing dye coupling, which is increased upon peripheral noxious stimulus. Dual patch-clamp recordings performed on dorsal root ganglia showed coupling between satellite glia cells with themselves, as well as with sensory neurons, suggesting it to be an essential bridge for the synchronization and activation of sensory neurons. [74] Recently performed studies also suggest that damage to Schwann cells has a role in neuropathic pain. [75]

Epigenetic Regulation in Neuropathic Pain Models

Epigenetic regulation is another important factor for selective resilience versus susceptibilities toward developing neuropathic pain. [76] Causal for this are remodelling processes and ensuing alterations in gene expression of chromatin due to enzymes like histone deacetylase (HDAC) or DNA methyltransferase (DNMT). Deregulation of those DNMTs and HDACs has been described in several neuropathic pain models and was found to regulate the expression of Potassium Voltage-Gated Channel Subfamily A Member 2 (KCNA2), a potassium channel, in peripheral sensory neurons after nerve injury, therefore contributing to hyperexcitability. [77, 78]

Another driver in epigenetic regulation is noncoding RNAs (ncRNAs), which exert immense posttranscriptional and translational control both in physiological and disease states. If nerve injury occurs, up to hundreds of micro RNAs (miRNA) can be down- or upregulated, leading to different outcomes like an overexpression of TNF-alpha, brain-derived neurotrophic factor (BDNF), or the transcription factor Stat-3. [79] Another study has shown that an upregulation of long noncoding RNAs (lncRNAs) after nerve injury led to the oppression of KCNA2 in sensory neurons. This further led to hyperexcitability again. [80]

Genetic Factors in Neuropathic Pain

Referring to a recent systematic review, variants in 28 genes involved in receptor signalling and binding, neurotransmission, immune response, drug metabolism, and iron metabolism displayed association with neuropathic pain. [81] Gain of function mutations in sodium channels like Nav1.7, Nav1.8, Nav1.9, and others have been linked to pain disorders, with Nav1.7 variations found in 30% and Nav1.8 in 9% of patients with idiopathic small-fiber neuropathy. [82–84]

Another example of a monogenetic pain disorder are gain-of-function mutations in TRPA1 causing familial episodic pain syndrome, while another study showed genetic variants in genes coding for TRPA1 and TRPV1 in patients with erythromelalgia. [81, 85]

In general, there is a need for more and larger studies to replicate the findings.

1.5.2 Diagnosis of Neuropathic Pain

Since both the cause and the symptoms of neuropathic pain can be very different, making the diagnosis is often difficult and therefore often made too late. Different diagnostic approaches deliver a broad range of sensitivity and specificity and should therefore be handled with caution regarding their significance.

Recognizing the challenges to determine the presence of neuropathic pain, NeuPSIG proposed a grading system to map the likelihood of neuropathic pain being present in comparison to the carried out examination, dividing it into three levels (see Figure 11). [86]

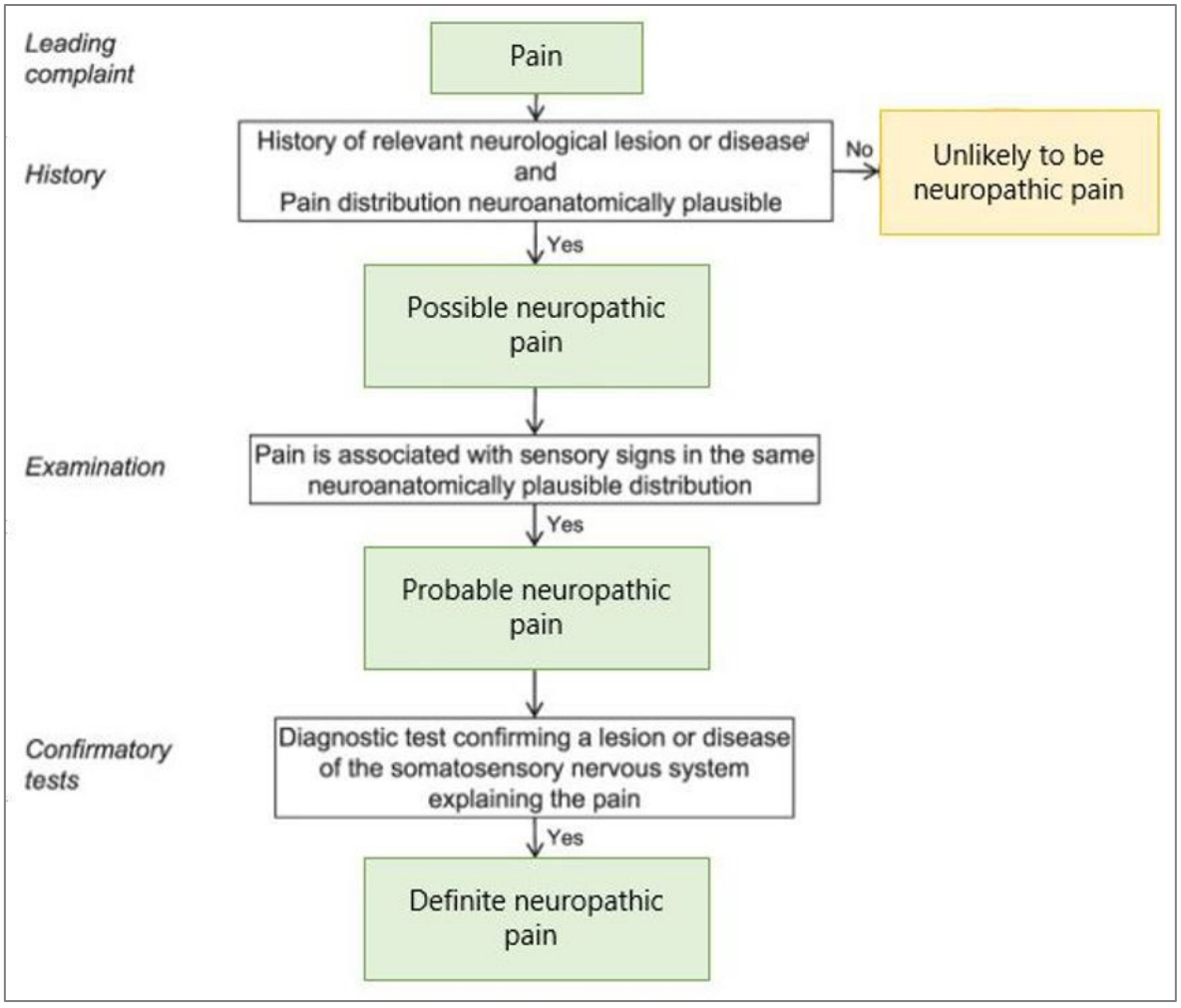

Figure 11: Grading system for neuropathic pain based on figure 2 in [86]

Possible Neuropathic Pain

As already mentioned above, neuropathic pain can present itself in various ways. Anyways, there is a typical set of pain descriptors like burning or hot, pricking or pins and needles, electric shocks, pain evoked on touching or cold, and nonpainful sensations like tingling and numbness that on their own aren't pathognomonic for neuropathic pain, but the presence of several descriptors is significantly more likely to be associated with neuropathic pain than other pain conditions. [86, 87]

Different screening tools, like Douleur Neuropathique en 4 questions [88] (DN4-Questionnaire), Pain DETECT [89], Neuropathic Pain Scale [90], McGill Pain Questionnarie-2 [91] and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) [92] to name just a few, have been developed in the past years with the aim to identify affected patients. [86]

At this point, it should be mentioned that screening tools may be helpful in general, but at a single-patient level, they may fail to classify some patients (false negative) on the one hand, or erroneously identify some patients (false positive) on the other hand. [86]

In addition to those self-report assessment tools, there also must be a history of a relevant disease or lesion of the somatosensory nervous system, like a traumatic nerve injury or an episode of acute herpes zoster. While the temporal relationship between the event and pain onset may vary from immediate to up to several months or even years depending on the underlying cause, in general, a close relationship strengthens the clinical suspicion. [86]

Also, the distribution of the pain should anatomically match the location of the suspected disease or lesion derived from the previously raised history. [86]

Probable Neuropathic Pain

To accomplish the second level of certainty, the suspicion must be confirmed by a clinical examination. This can be done within the framework of a basic bedside examination targeting the different modalities listed in Table 2:

Modality	Bedside assessment	Affected fibers
Touch	Cotton bud/ball, painters` brush	A-beta fibers
Pinprick	Pin, toothpick, cocktail stick	A-delta fibers
Warm	Warm metal, tube with warm water	A-delta fibers C-fibers
Cold	Cold metal, tube with cold water, cloth with surgical spirit	A-delta fibers C-fibers
Vibration	Tuning fork	A-beta fibers

Table 2: Bedside sensory examination.

The presence of negative sensory phenomena like partial or full loss of one or several described modalities carries more weight than the presence of positive sensory phenomena like hyperalgesia or allodynia alone. This is because positive signs are also typically seen in patients with other pain conditions like pain of unknown origin, inflammatory pain, sleep deprivation, and anxiety. Further, it is also affected by negative emotions and stress. [86, 93, 94] Negative signs may also occur in nociceptive pain, however, they lack anatomically distinct borders and also are not reproducible. [95]

To further improve the significance of diagnostic tools and also being able to characterize the somatosensory phenotype of neuropathic pain in patients, a standardized quantitative sensory testing (QST) protocol was developed by the German Research Network on Neuropathic Pain in 2006. [96] QST uses a battery of thermal and mechanical stimuli to assess both plus (gain of function) and minus (loss of function) signs in specific body regions all in reference to gender- and age-matched values from 180 healthy subjects. [96]

Definite Neuropathic Pain

The third level of certainty requires confirmation via an objective diagnostic test. Different tests can be used depending on the underlying cause. Imaging techniques like magnetic resonance imaging (MRI) or computed tomography (CT) can confirm spinal cord injury, multiple sclerosis, nerve lesion, or stroke. Skin biopsy can be used to confirm a reduction of intraepidermal nerve fiber density.

Neurophysiological tests like contact heat evoked potentials (CHEPs) and laser evoked potentials (LEPs), nerve conduction velocity, R1 blink reflex, microneurography, and nerve conduction velocity can show neural function compromise. [86]

Hereditary neuropathic pain disorders can be diagnosed with genetic testing. No further diagnostic tests are necessary in cases of verified intraoperative nerve lesions or amputations. [86]

It is important to note that even at the third level of certainty, other conditions like tissue inflammation may partially or even fully explain the pain. This being the case, being classified with definite neuropathic pain means, that by using the patient`s history, clinical examination, and objective testing, present pain can but does not have to be explained by a neurological lesion or disease. [86]

1.5.3 Treatment of Neuropathic Pain

Many drug classes are currently being explored and researched for the treatment of neuropathic pain, as it poses challenges and typical analgesics like NSAIDs are becoming less effective. The following chapter will discuss the most recent data on pharmacotherapy for neuropathic pain, based on the recommendations of the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain made in 2015 as well as more recent guidelines of the German Society for Neurology published in 2019. [97, 98]

The recommendations of the NeuPSIG are derived from a comprehensive systematic review and meta-analysis of 229 studies, focusing on the primary measure of the number needed to treat (NNT) to achieve 50% pain relief. The review encompasses various drug classes, including tricyclic antidepressants (TCAs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), anticonvulsant drugs, opioids, cannabinoids, capsaicin, lidocaine, and botulinum toxin (BTX-A). [97]

Oral Treatment

TCAs are antidepressant drugs that inhibit the neuronal reuptake of serotonin and norepinephrine in the central nervous system and block the receptors of the transmitters serotonin, norepinephrine, and acetylcholine, among others. The exact mechanism of action of their analgesic efficacy remains unclear, but it is thought that serotonergic and noradrenergic neuromodulation leads to an indirect modulation of the opioid system of the brain downstream. [99]

Major adverse effects of TCAs are sedation, confusion, cardiac conduction block, anticholinergic effects (e.g., constipation, blurred vision, dry mouth, and urinary retention), weight gain, and orthostatic hypotension. [87]

In 15 placebo-controlled trials with 948 participants, evaluating mainly amitriptyline at doses between 25-150 mg per day with no evidence for a dose-response effect, the combined NNT was 3,6 (3,0–4,4) and the NNH was 13,4 (9,3–24,4) with a moderate final quality of evidence. [97]

SNRIs are also antidepressant drugs that specifically inhibit the reuptake of serotonin and norepinephrine in presynaptic neurons and thus increase the extracellular concentration of serotonin and epinephrine. [100]

Major adverse effects of SNRIs are nausea, constipation, loss of appetite, sedation, hyperhidrosis, dry mouth, and anxiety. [87]

14 studies, including 2541 participants, of which nine used duloxetine (20–120 mg per day) and four used venlafaxine (150–225 mg per day), reached the result of a combined NNT of 6,4 (5,2–8,4) and a NNH of 11,8 (9,5–15,2) with a high final quality of evidence. [97]

In vitro binding studies showed that duloxetine was around three times more potent at inhibiting serotonin uptake than norepinephrine uptake. [101] Duloxetine also modulates pain by activating different cerebral prefrontal areas, increasing dopamine occurrence in the prefrontal cortex, and modifying spinal pain pathways. Further, an antinociceptive effect of duloxetine is seen through the inhibition of Nav1.7 Na+ channels and interaction with local anaesthetic receptors, reducing spontaneous nerve impulses resulting from the peripheral injury. [102]

Another very well-studied drug class for neuropathic pain are **Antiepileptics**, with pregabalin and gabapentin being the main active agents under research focus. [103, 104] Both lead to significant beneficial effects on symptoms of neuropathic pain, while usage also significantly increases the number of adverse events. [103, 105] A total of 18 RCTs with a combined NNT of 7,7 (6,5–9,4) and a NNH of 13,9 (11,6–17,4) have been identified for pregabalin (150–600 mg per day). Further, a dose response gradient with higher doses following a higher response in patients could be seen. For gabapentin, a total of 14 RCTs with 900–3600 mg per day and 6 RCTs with gabapentin ER respectively gabapentin enacarbil 1200–3600 mg per day were identified. The combined NNT was 6,3 (5,0–8,3) for gabapentin and 8,3 (6,2–13) for gabapentin ER/enacarbil. The NNH was 25,6 (15,3–78,6) for gabapentin and 31,9 (17,1–230) for gabapentin ER/enacarbil. Both drugs have a high final quality of evidence. [97]

Major adverse effects of antiepileptics are sedation, weight gain, dizziness, edema, and blurred vision. [87]

Opioids have already been presented in the pharmacotherapeutic treatment of OA. (see Chapter B 2.6) They are the oldest drug class for pain and in general highly effective, but in chronic neuropathic pain, their analgesic efficacy is subject to considerable uncertainty. [106]

Major adverse effects of opioids are sedation, respiratory depression, hypotension, miosis, nausea and vomiting, increased sweating, itching, constipation, urinary retention, development of opioid tolerance and dependence, and thoracic rigidity. [107]

Tramadol is a mild opioid that induces its analgesic effects through different targets on the serotoninergic system, the noradrenergic system, and opioid receptors. Seven studies addressing the effectiveness of mainly tramadol ER with doses up to 400 mg per day and a moderate final quality of evidence came to a combined NNT of 4,7 (3,6–6,7) and NNH of 12,6 (8,4–25,3). [97]

Oxycodone is a semi-synthetic, strong opioid, that is a highly selective mu-opioid receptor agonist but influences NMDA receptors as well, probably being causal for their effectiveness in neuropathic pain.

Ten trials using mainly oxycodone (10–120 mg per day) and morphine (90–240 mg per day) came to a combined NNT of 4,3 (3,4–5,8) and a NNH of 11,7 (8,4–19,3). There seemed to be an association for maximum effectiveness with 180 mg of morphine or equivalent doses of oxycodone, with no additional benefit for higher doses. [97]

Cannabinoids are a growing body of research for therapeutic use in many different diseases, including Alzheimer´s disease, Parkinson´s disease, multiple sclerosis (MS), schizophrenia, and also neuropathic pain. They mediate their effect primarily through various cannabinoid receptors on the endogenous cannabinoid system (ECS). But since different plants of cannabis also have a different composition and contain a variety of non-cannabinoids, terpenes and flavonoids that add their own pharmacological properties, there is an urgent need for further research to better understand the biochemical and molecular effects of cannabis to fully understand its implications as a pharmaceutical drug. [108]

Major adverse effects of cannabinoids are nausea and vomiting, tachycardia, vasodilatation with conjunctival injection, increased appetite, dry mouth, feelings of anxiety up to paranoid experiences and feelings of panic, and psychotic symptoms. Long-term consequences of chronic usage include an increased risk of comorbid mental disorders like affective disorders and schizophrenia as well as an increased risk of pulmonary diseases if inhaled. [108, 109]

Nine trials have been identified using Sativex in neuropathic pain and two in pain associated with MS. It is an oromucosally delivered spray that includes extracts from sativa cannabis (standardized 27mg/ml delta-9-tetrahydrocannabinol and 25 mg/ml cannabidiol). Out of those only three trials were positive with no further description of the results. [97]

Topical Treatment

Capsaicin is a TRPV1 receptor agonist. Capsaicin patches are a topical alternative for systemic therapy in which a mostly high-concentration capsaicin patch (8%) is applied to the skin for one hour, leading to a local, burning pain lasting approximately two to three days in the sense of thermal hyperalgesia. This leads to a reduction or loss of function of the capsaicin receptors, which in turn

results in pain relief. It takes about three months until the receptors are fully developed again, and the effect wears off. [110, 111]

Major adverse events are hypersensitivity reactions of the skin (e.g., urticaria, blisters, or vesicles) at the site of application, stinging, and itching. [110]

The IASP identified five studies with a combined NNT of 10,6 (7,4–19) with a high final quality of evidence. It should be noted that the long-term safety for repeated usage of high-dose capsaicin patches has not been clearly established yet, particularly with focus on the degeneration of epidermal nerve fibers. This may be a concern in the treatment of progressive neuropathy. [97]

Lidocaine is a local anaesthetic that acts by prolonging the blockade of voltage-gated na+ channels, which are responsible for the propagation of action potentials. In general, 5% lidocaine patches are placed directly over the area of pain in patients with local limited neuropathic pain over the course of twelve hours per session. The advantage of lidocaine patches is that they have little to no side effects in comparison to pregabalin or other commonly used drugs for neuropathic pain. [112] Due to the inclusion criteria of the IASP with a minimum last of three weeks` in duration, no study could be included into the analysis, but studies with less than three weeks` duration showed efficacy of the treatment while having excellent safety and tolerability. [97]

Botulinum Toxin is another option for topical therapy of neuropathic pain. The neurotoxins irreversibly inhibit the release of acetylcholine from the presynapse into the synaptic cleft at peripheral nerve terminals. In therapy, it is infiltrated subcutaneously or intracutaneously over a large area in the painful area and leads to an analgesic effect for up to 12 weeks. [113]

Major adverse events are temporary muscle weakness, local pain resulting from the injection, dry mouth, and hematomas. [114]

Four RCTs evaluating the efficacy of a single dose administration of BTX-A (using 50–200 units subcutaneously in the area of pain) showed a positive primary outcome with a combined NNT of 1,9 (1,5–2,4), a very low placebo effect and excellent general safety. [97]

Combination Therapy

Different results can be derived from seven identified RCTs with different combination therapies. Two of the studies showed superiority of combination therapy of gabapentin with morphine or nortriptyline over monotherapy with higher doses and no additional side effects. However, the largest study showed no difference in efficacy or side effects of pregabalin in combination with duloxetine at moderate doses (300 mg pregabalin and 60 mg duloxetine daily) versus monotherapy at high doses (600 mg pregabalin and 120 mg duloxetine) in patients who did not respond to monotherapy at moderate doses. [97]

In general, a re-evaluation of the therapy should first be made after four to six weeks and if there is no response, the monotherapy dose should be increased. After a persistent non-response over further four to six weeks, combination therapy should be initiated. [97]

Grade classification	Drugs	Dosage and dose regime	Recommendations
Strong for	Gabapentin Gabapentin ER/enacarbil Pregabalin SNRIs Duloxetine Venlafaxine TCAs	1200–3600 mg TID 1200–3600 mg BID 300–600 mg BID 60–120mg QD 150–225 mg QD 25–150 mg QD/BID	First-line First-line First-line First-line First-line
Weak for	Capsaicin 8% patches Lidocaine patches Tramadol BTX-A Strong opioids	1–4 patches to painful area for 30–60 min every 3 months 1–3 patches to painful area for up to 12 hours 200–400mg BID (tramadol ER) or TID 50–200 units to painful area every 3 months Individual titration	Second-line (PNP) Second-line (PNP) Second-line Third-line Third-line
Inconclusive	Combination therapy Capsaicin cream Carbamazepine Clonidine topical Lacosamide Lamotrigine NMDA antagonists SSRI antidepressants Tapentadol Topiramate Zonisamide		
Weak against	Cannabinoids Valproate		
Strong against	Levetiracetam Mexiletine		

Table 3: List of drugs with their recommended dosage and dose regime for neuropathic pain based on the latest recommendations of the NeuPSIG, ordered by their grade of indication. [97]

The german society for neurology have published a current guideline for diagnosis and non-interventional therapy of neuropathic pain together with the austrian -, and swiss society for neurology, as well as the german pain society and the german society for psychological pain therapy and research in 2019. [98] Pharmacotherapeutic recommendations in this guideline are similar to those of the NeuPSIG of the international association for the study of pain, still, they made some changes, described in Table 4. Venlafaxine dropped from a first-line treatment option to not being recommended any more due to an insufficient data situation. Further, NSAR, COX-2-inhibitors, paracetamol, Metamizol, SSRI´s, Alpha lipoic acid, NMDA-receptor antagonists, Baclofen, Benzodiazapines, Lacosamid, Phenytoin, Levetiracetam, Topiramat, Milnacipran, NaSSA, topical amitriptyline ointment and transcutaneous electrical nerve stimulation (TENS) are not recommended anymore. The use of Oxycarbazepin, Lamotrigin, and Cannabinoids could be considered in individual cases. [98]

Recommendations	Drugs
First-line	Gabapentin/Pregabalin TCA Duloxetin
Second-line	Capsaicin patches Lidocain-Patches
Third-line	Weak and strong Opioids BTX-A
Not recommended	NSAIDs/COX-2-inhibitors, Paracetamol, Metamizol SSRI[5] (Citalopram/Escitalopram, Fluoxetin, Fluvoxamin, Sertralin) Venlafaxine Cannabinoids Alpha lipoic acid NMDA receptor antagonists Baclofen Benzodiazepine Lacosamid Phenytoin Levetiracetam Topiramat Milnacipran NaSSA[1] Topical application of amitriptyline ointment TENS[2]

Table 4: Recommendations for the pharmacotherapy of neuropathic pain by the German guidelines [98],
[1] = noradrenergic and specific serotonergic antidepressant, [2] = transcutaneous electrical nerve stimulation

Furthermore, a clinical pathway for the treatment of neuropathic pain was published within the framework of the guideline. The primary focus is on careful diagnosis and comprehensive patient education about both the disease and treatment options. If possible, a causal therapy should be implemented. Alternatively, or in combination with this, pharmacotherapy with first- or second-line drugs should be used. In individual cases, this can be supplemented with third-line therapy options. In the case of severe pain, when a rapid onset of action is required, and in the case of mixed neuropathic and nociceptive pain, a combination therapy with opiates, as described in Figure 12, is recommended. [98]

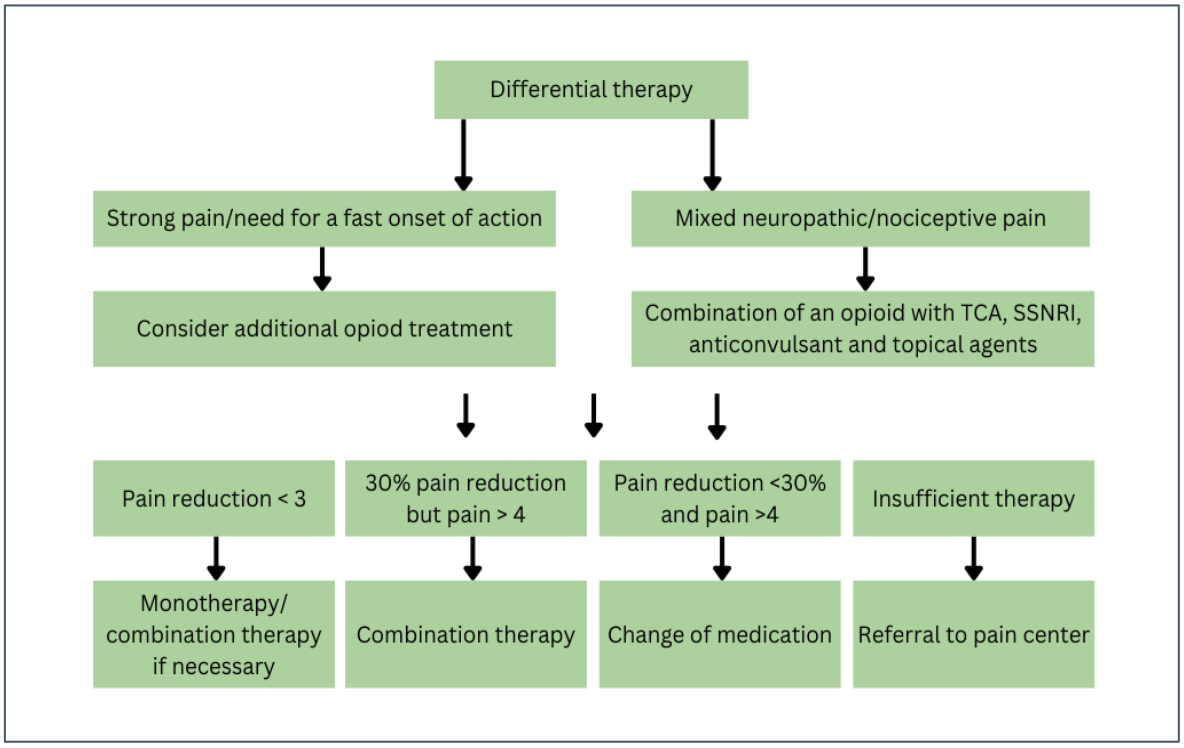

Figure 12: Clinical pathway for the treatment of neuropathic pain in cases of severe pain/need for a fast onset of action or mixed neuropathic/nociceptive pain based on [98]

Finnerup et al. further investigated the effectiveness of drugs recommended by the NeuPSIG. They analysed clinical trials on neuropathic pain conducted over the past 35 years and concluded, that the NNT has increased across all drug classes, indicating a decrease in estimated drug effectiveness over time. (see Figure 13) This decline in drug effect sizes can be attributed to several factors, including altered study design, longer study duration, changes in study size, and modifications in the reporting of findings. Notably, placebo responses did not

demonstrate a consistent increase over time, except for early trials with very low responses. Furthermore, higher placebo responses were associated with a higher NNT. [115]

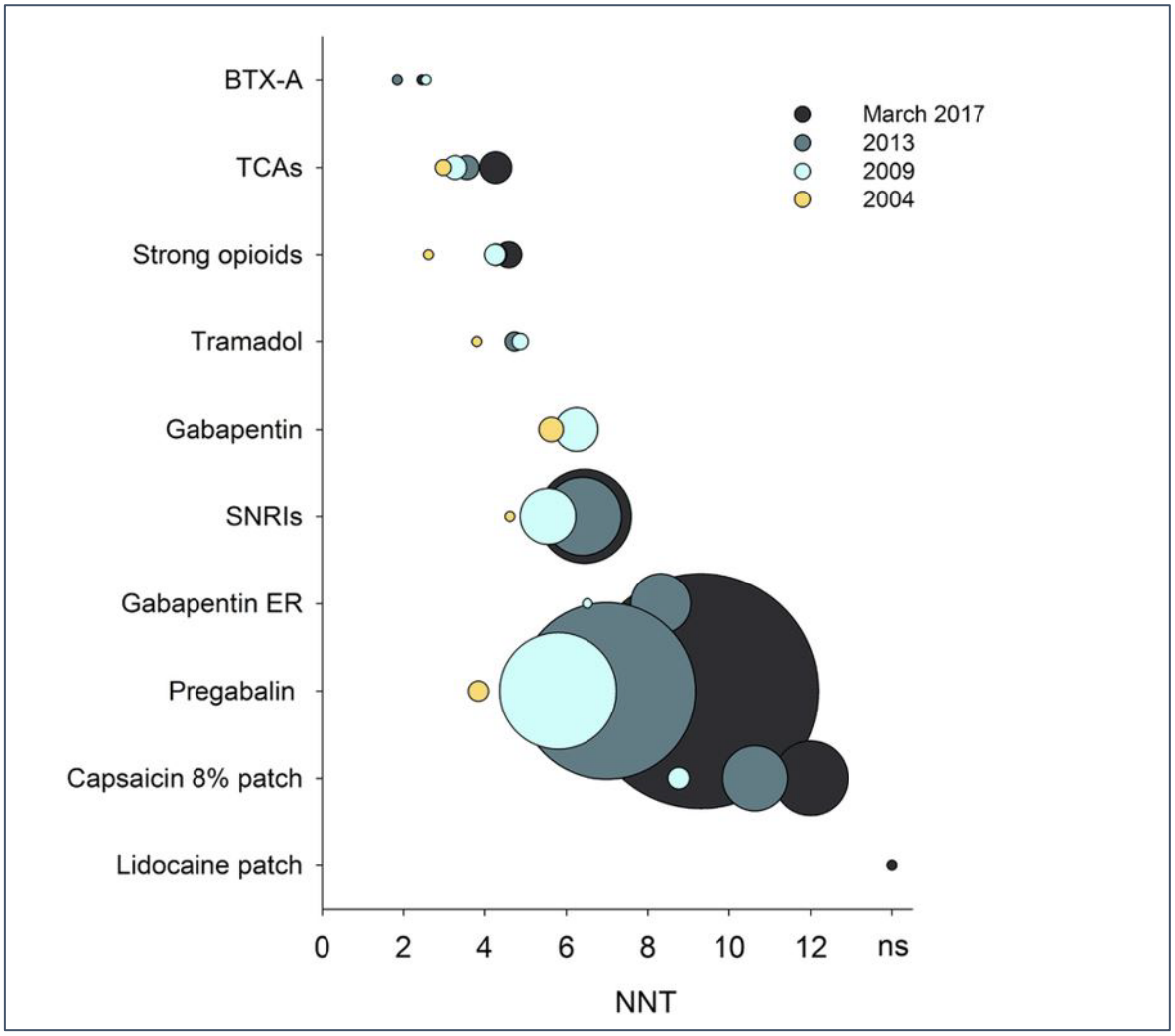

Figure 13: Different drug classes and their effectiveness described in NNT compared over the years 2004 (yellow), 2009 (turquoise), 2013 (grey), and 2017 (black) based on Figure 5 in [115]

2 Materials and Methods

The aim of this prospective clinical randomized trial was to see if patients at disproportionate risk for developing CPSP could be identified preoperatively. Therefore, patients included in the study underwent several specific screening tools (further explained in this chapter), anamnesis, and check-up of data history in the openMEDOCS system of the Styrian Hospital Society (KAGes). Focus was set on pre-existing chronic pain and the use of analgesics and/or co-analgesics, and a clinical examination focusing on the presence of hyperalgesia or allodynia. Afterwards, they were separated into a high risk and a low risk group. The classification into the two groups was then performed together with two experienced senior physicians from our clinic´s Department of Anaesthesiology and Pain Medicine. Clinical outcomes as well as patients´ satisfaction were subsequently controlled in follow-ups made on the second postoperative day, the discharge day, after six weeks, three months, and six months.

2.1 Patients

All Patients recruited in this study received a TKA at the Department of Orthopaedics and Traumatology of the Medical University of Graz between March 2021 and July 2021. They were informed in detail about the procedure of the study, then had to sign a written informed consent and pass the inclusion and exclusion criteria listed below:

Inclusion Criteria:

- Patients with a minimum age of 18 years
- Inpatient stay at the orthopaedic ward due to elective surgery (TKA).
- Analgesic therapy is required by the patients
- Test persons speak and understand German fluently
- Subjects give written consent to participate in the study

Exclusion Criteria:

- Limited capacity to consent (known psychiatric illnesses, dementia).
- Parallel study, which is an interference.
- Care provided in the context of a polytrauma

2.2 Data Collection and Examinations

Each patient got an ID on an encrypted data cloud (RedCap®) licensed to the Medical University of Graz. Patient-identifying data are stored separately in an encrypted Excel file ("patient-identificaction log"). Data collection and storage of pseudo-anonymized patient data are also performed via RedCap®.

The Medical University of Graz provided two tablets with the system installed on them that were used for data collection. If patients were able to, they were explained how to work with the tablet in detail and filled out the questionnaires by themselves, otherwise, data was collected by an examiner (cand. med. Danijel Colovic). Study-specific patient data like names, dates of birth, telephone numbers, addresses, and medical histories was collected via the openMEDOCS system of the Styrian Hospital Society (KAGes).

In the initial, preoperative examination, patients were asked to answer questions regarding their demographic-, injury-specific- and treatment-specific data and to complete all patient-reported outcome measures (PROMs, further described in chapter 2.3).

Demographic data contained Date of birth, gender (male, female, other), height, weight, BMI, education level (in years), occupational status, family status, housing situation, smoking habits, alcohol consumption, annual gross salary, and date of inpatient admission.

Injury-specific data contained reason for inpatient stay, association of the injury with trauma, time of illness or onset of pain, type of illness, duration of the disease, side of the disease, conservative therapy attempt, medication on demand, type of referral (self-referral, referral from a general practitioner or referral from a specialist), affected body regions, waiting time for preoperative anaesthetic examination and surgery.

Treatment-specific data contained surgical technique (access, duration, surgeon, and implant) and anaesthesiologic procedure (general anaesthesia and regional anaesthesia).

As part of the examination, all patients were tested for the presence of allodynia, which is defined as pain due to a normally non-painful stimulus and is a common

symptom of neuropathic pain. [117] Its occurrence was measured by the appearance of mechanical pressure in the area of pain with both a blunt and a sharp object using the blunt and sharp sides of a cotton swab. Further, the ROM of the affected knee was examined both actively and passively using a goniometer for measuring. All examinations were performed by an examiner (cand. med. Danijel Colovic) under supervision.

Follow-ups were conducted on the second postoperative day and the discharge day in person during the postoperative hospital stay, at six weeks, three months, and six months either in person at a control examination, through the distribution of self-report questionnaires, or via telephone calls if patients were unable to attend an on-site appointment or complete the self-report questionnaires for any reason. Table 5 displays the measurement times for the various questionnaires. It should be noted, however, that not all questionnaires were answered by all study participants at every survey time.

	Preoperative	**2 day post-op**	**Discharge**	**6 Weeks**	**3 months**	**6 Months**
NRS	x	x	x	x	x	x
Allodynia	x	x	x	x		
Hyperalgesia	x	x	x	x		
Range of Motion	x			x	x	x
FSQ	x	x	x	x	x	
DN4-questionnaire	x	x		x		
KOOS	x			x	x	x
WOMAC	x			x	x	x
SF-36	x				x	x
PCS	x					
HADS	x					

Table 5: Timetable for each examination. NRS = numeric rating scale, FSQ = Fibromyalgia survey questionnaire, DN4 Questionnaire - Douleur Neuropathique en 4 questions, KOOS = Knee Injury and Osteoarthritis Outcome Score, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, SF-36 = Short form 36, PCS = Pain catastrophizing scale, HADS = Hospital anxiety and depression scale.

2.3 Patient-Reported Outcome Measures (PROMs)

Patient-Reported Outcome Measures (PROMs) are questionnaires aimed at patients. They offer the possibility to survey the subjective perception of patients regarding symptoms, the state of health and its influence on the personal quality of life, as well as the satisfaction with the treatment in a standardized way. In addition, the use of PRO instruments in clinical practice allows an assessment of the course of symptoms, monitoring of therapy steps taken and, subsequently, their optimization. [118]

In the context of gonarthrosis, PRO instruments can contribute to the assessment of the course of the disease in both the early and late stages and are therefore invaluable tools for clinical care and shared decision-making with patients. [118, 119]

2.3.1 WOMAC Index

Researchers developed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) in 1982, and it has become one of the most utilized PRO instruments, particularly in individuals with knee or hip osteoarthritis. [120] The questionnaire has been successfully translated into German and its computerized version has also been validated and shown to be reliable. [121, 122]

The questionnaire comprises 24 questions, encompassing multiple dimensions. Among them, five questions assess patient pain conditions, two focus on movement reduction and stiffness, and the remaining 17 pertain to the function dimension, evaluating the level of difficulty experienced in various activities. [120]

There are three available versions of the score. The first version utilizes an ordinal scale, allowing patients to rate questions on pain, stiffness, and physical function using five levels ranging from "none" to "extreme". The second version employs a visual analog scale. Lastly, the third version employs a numerical rating scale, where each question is answered with a numerical value ranging from 1 ("no complaints") to 11 ("extreme complaints"). The third version was utilized in the current study. [120]

The WOMAC score has been widely validated. Weak evidence for the stiffness subscale and weaknesses in detecting changes in physical function in the progression assessment are under discussion. [120]

2.3.2 Knee Injury and Osteoarthritis Outcome Score (KOOS)

Roos et al. developed and published the Knee Injury and Osteoarthritis Outcome Score (KOOS Score) in 1998 to accurately evaluate the functional status and quality of life of patients at higher risk of developing osteoarthritis due to various knee injuries, such as anterior cruciate ligament (ACL), meniscus, or cartilage injuries. [123] It is a patient-reported outcome (PRO) instrument that includes 42 questions in the following 5 dimensions illustrated in Table 6: [123]

Dimensions	Number of Questions
Pain	9
Symptoms	7
Activities of daily living	17
Functionality during sports and leisure activities	5
Quality of life associated with the affected knee	4

Table 6: Dimensions of the KOOS

2.3.3 The Pain Catastrophizing Scale (PCS)

The Pain Catastrophizing Scale (PCS) assesses the extent to which patients tend to overestimate their health limitations or to "catastrophize" them. The questionnaire consists of 13 questions, in which, for example, the feeling of helplessness, an overestimation of pain events, or recurring thoughts of pain are asked. [124] Studies validated its specifically in the context of gonarthrosis. [125] For each question, patients can assign scores ranging from zero to four, leading to a maximum achievable score of 52. A higher number of points indicates a greater tendency for the individual to overestimate pain events. [124]

2.3.4 Douleur Neuropathique en 4 Questions (DN4 Questionnaire)

The DN4 questionnaire is a short questionnaire to identify neuropathic pain. In this assessment, patients respond to 10 questions regarding the type, location, and accompanying symptoms of pain, with options to answer either "yes" or "no". A positive test result is determined if the patient answers more than 4 questions with "yes". According to the literature, the questionnaire exhibits a sensitivity of 83% and specificity of 90%. [88]

2.3.5 Short Form 36 (SF-36)

The SF-36 is a widely utilized PRO instrument for evaluating health-related quality of life. The first version of this questionnaire was developed in 1988 as a revised edition of the Short Form 20 score. A subsequent revision in 1996 led to the creation of the second version. Currently, the SF-36 is accessible in over 170 languages globally and finds application across diverse medical specialties. [126]

Disadvantages arise from the length of the questionnaire, where it is assumed that patients need about seven minutes to complete it. This circumstance plays a subordinate role in research but comes into play in everyday clinical practice. [126]

The SF-36 contains 36 questions from eight different dimensions, listed in Table 6:

Dimension	Number of Questions
Physical health	10
Limited physical-related role function (role physical)	4
Limited emotional-conditional role function (role emotional)	3
Energy/fatigue	4
Mental health	5
Social functioning	2
Pain	2
General health	5

Table 7: Dimensions of SF-36

Apart from the overall evaluation, the aspects relating to mental health (Mental Component Summary) and physical health (Physical Component Summary) can also be calculated and evaluated separately as sum scores. This separate analysis is particularly important in orthopedics, as the level of physical health in this field is often significantly lower than that of mental health. [127]

2.3.6 Numeric Rating Scale (NRS)

The Numeric Rating Scale (NRS) serves as a commonly employed score to measure subjective pain perception. Patients can quantify their personal pain experience on an 11-point Likert scale, assigning a number between 0, indicating "no pain," and 10, representing the "strongest pain imaginable". [128]

2.3.7 Hospital Anxiety and Depression Scale (HADS)

The HADS is a questionnaire divided into two subgroups, measuring symptoms of depression (HADS-D) and anxiety (HADS-A). [129] The test consists of 14 questions, seven of which relate to anxiety and seven to depression. Questions are presented thematically in alternating order. There are scores from 0 to 3 for each answer that can be added in the evaluation process. It is important to evaluate the scores separately. Scores from 0–7 should be interpreted as non-cases, 8-10 as mild, 11–14 as moderate, and 15–21 as severe cases. [130]

Literature describes that a cut-off score of 8 has a specificity of 0.79 and a sensitivity of 0.83 for depression and a specificity of 0.78 and a sensitivity of 0.9 for anxiety. [129]

2.3.8 Fibromyalgia Survey Questionnaire (FSQ)

The FSQ is a questionnaire for the evaluation of fibromyalgia syndrome. Patients are asked several specific questions about the symptoms of fibromyalgia, which are answered on a four-point scale (from "not present" to "very pronounced"). The higher the sum of the answers, the higher the probability of the presence of fibromyalgia syndrome. [131]

2.4 Statistical Evaluation

The evaluation is carried out using descriptive statistics and statistical tests (Student's t-test, Pearson's correlation analysis). All determined data was converted and collected in a Micorsoft Excel® spreadsheet. The statistical analysis of the data was done with the help of IBM® SPSS® Statistics Version 23. The determined factors were frequencies, mean values, and standard deviation (SD). Furthermore, Student's T-test was used for the comparison of connected and independent samples. The Mann-Whitney U test was used for independent samples that did not meet the requirements for a t-test. A p value ≤ 0.05 was considered significant.

To evaluate within-subject effects, repeated-measures analysis of variance was done. Results were only evaluated, if sphericity was given due to a non-significant Mauchly-W test ($p > 0.05$). However, if the Mauchly-W test was significant ($p \leq 0.05$), degrees of freedom were adjusted by multiplying them with a correction factor Epsilon (ε). The Greenhouse-Geisser correction was used if its epsilon was below 0.75, and the Huynh-Feldt correction was used if it was above 0.75.

To describe the individual effect of a variable, effect strength after Cohen (1992) was calculated and further classified according to Cohen's (1988) classification guide ($f \leq 0.10$ corresponds to a weak effect, $f \geq 0.25$ corresponds to a medium effect, $f \geq 0.40$ corresponds to a strong effect).
To further differentiate when significant differences between the within-subject variables occurred, Bonferroni-corrected pairwise comparisons were used.
All results were rounded to three decimal places.

2.4.1 Missing Data

Missing data can cause problems in data analysis. Ideally, missing data is avoided or mitigated as best as possible. To minimize missing data, RedCap® performed a check for each assessment and thus, missing data was immediately pointed out. Still, it could not be completely avoided, in which case the strategy of multiple imputations was applied.

3 Results

Initially, a total of 72 patients underwent eligibility assessment for inclusion in the study. Of these, nine patients declined participation, and two patients were excluded due to language barriers. Subsequently, 61 patients met the inclusion criteria and were enrolled in the study. During the study period, two patients withdrew within the first week, four patients were lost to follow-up, and five patients discontinued participation due to complications during the rehabilitation process. Eventually, the final sample size consisted of 50 patients, comprising 31 females (62%) and 19 males (38%). Among the participants, the high-risk group consisted of 20 patients (40%), with 16 females (80%) and four males (20%). Conversely, the low-risk group comprised 30 patients (60%), evenly distributed with 15 females (50%) and 15 males (50%) (see Figures 14 and 15).

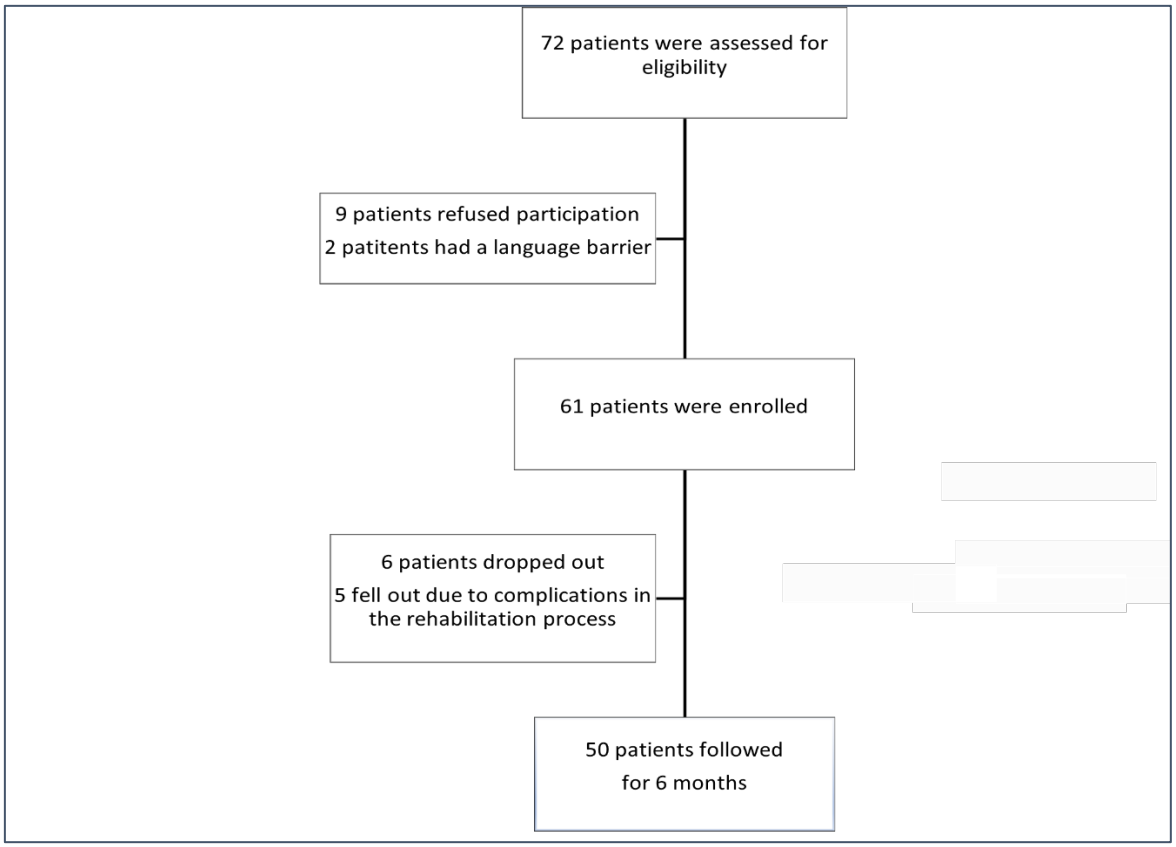

Figure 14: Flowchart of the included patients

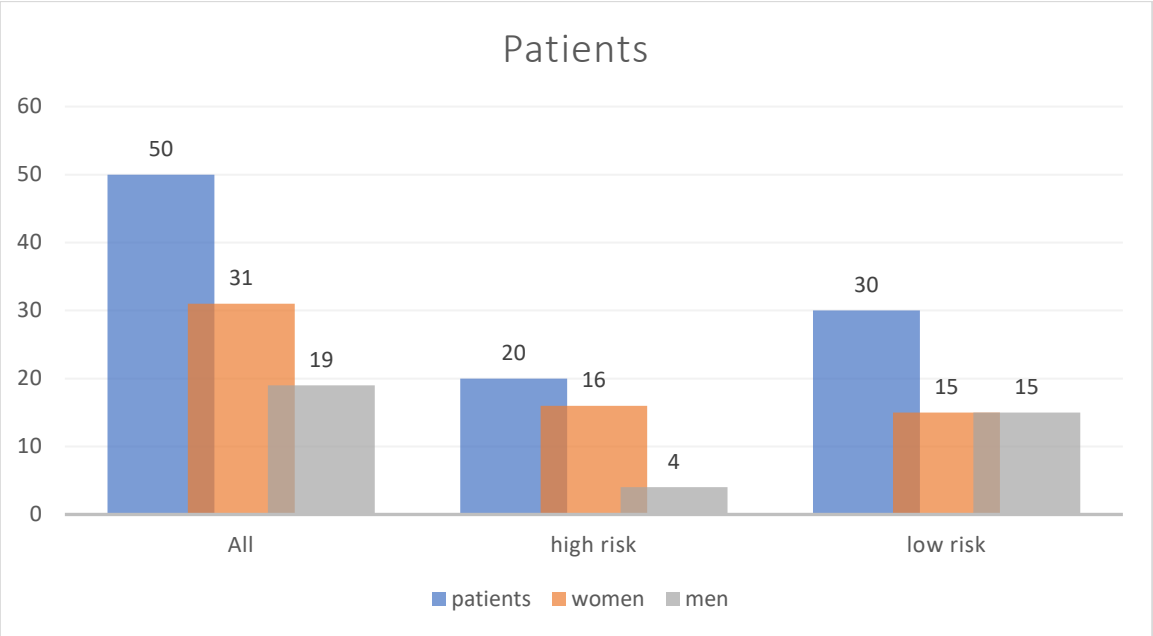

Figure 15: Gender division of all patients (31 women, 19 men), the high risk group (16 women, 4 men), and the low risk group (15 women, 15 men)

The analysis of age data revealed that the cohort had a median age of 67, with the minimum age being 52 and the maximum age reaching 87. The first quartile (Q1) was calculated as 56, while the second quartile (Q2) was determined to be 75. Moreover, within the high-risk group, the median age was 70, with the minimum age recorded as 52 and the maximum age as 83. The first quartile (Q1) for this group was 56, and the second quartile (Q2) was 75. Similarly, the low-risk group exhibited a median age of 66, with the minimum age being 53 and the maximum age reaching 87. The first quartile (Q1) for this group was 56, and the second quartile (Q2) was 75. We have visualized these findings in Figure 15.Age data were collected for all patients, including the entire cohort (Median = 67, minimum = 52, maximum = 87, Q1 = 56, Q2 = 75), the high-risk group (Median = 70, minimum = 52, maximum = 83, Q1 = 56, Q2 = 75), and the low-risk group (Median = 66, minimum = 53, maximum = 87, Q1 = 56, Q2 = 75) (see Figure 16).

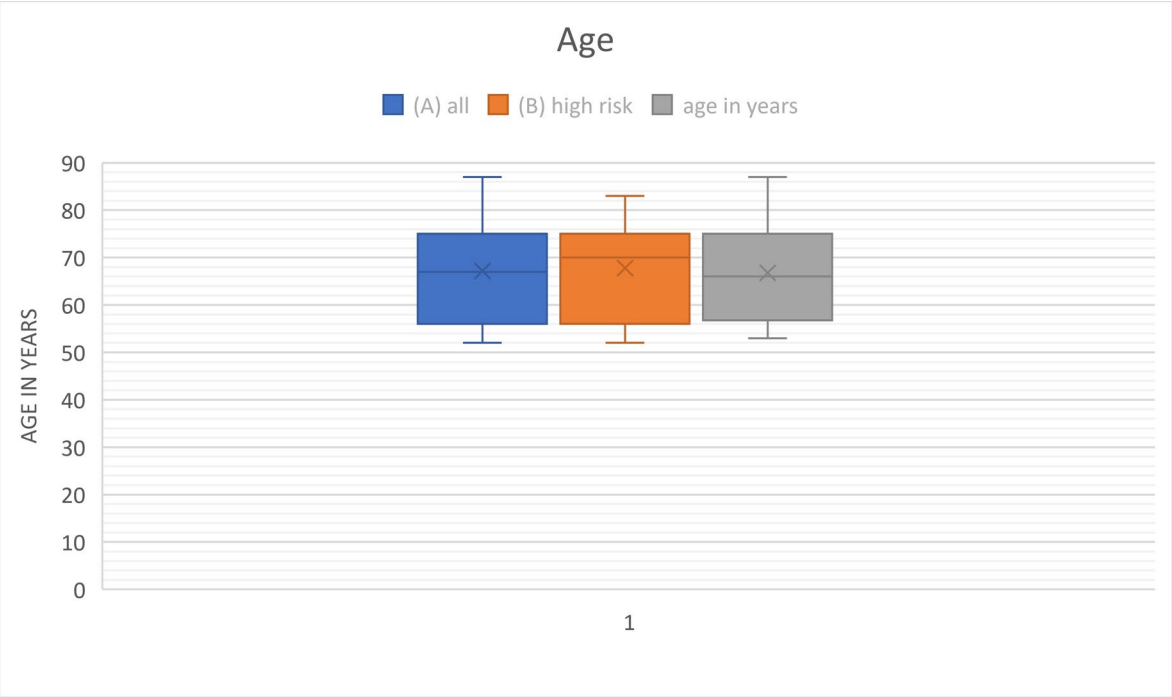

Figure 16: Boxplot comparing the preoperative age of all patients (A), the high risk group (B), and the low risk group (C).

Preoperatively, precise measurements of the BMI were documented for all participants within the study, encompassing the complete cohort as well as the distinct high-risk and low-risk subgroups. These BMI values, serving as a quantitative indicator of the individuals' body composition, contribute to a comprehensive understanding of their preoperative characteristics and potential implications for the surgical intervention under investigation. The BMI distribution within the cohort exhibited a median value of 31.79, with the minimum value being 22.72 and the maximum value being 42.37. The first quartile (Q1) was calculated to be 28.7, while the second quartile (Q2) stood at 34.32. Additionally, outliers were identified at 44.30 and 44.64. Moreover, the high-risk group displayed a median BMI of 29.7, ranging from a minimum value of 22.72 to a maximum value of 36.51. The first quartile (Q1) for this group was 26.25, and the second quartile (Q2) was 33.17. Likewise, the low-risk group exhibited a median BMI of 32.08, with the minimum value recorded as 23.25 and the maximum value as 44.64. The first quartile (Q1) for this group was 28.8, and the second quartile (Q2) was 36.36. (see Figure 17)

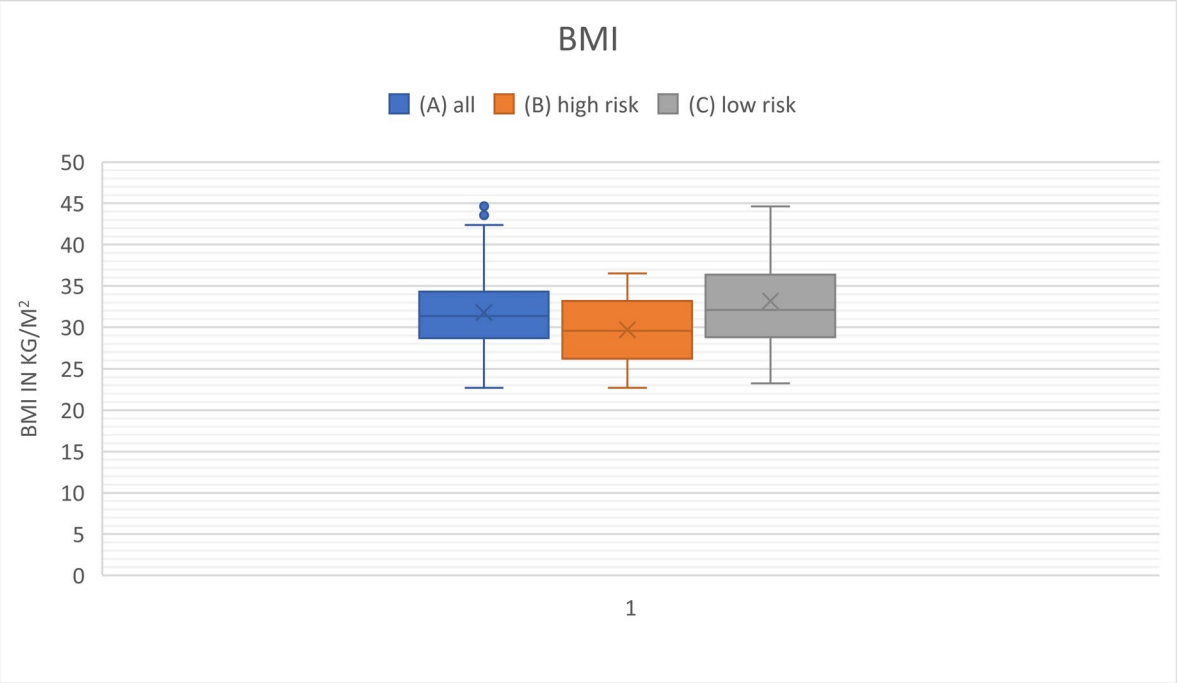

Figure 17: Boxplot comparing the preoperative BMI of all patients (A), the high risk group (B), and the low risk group (C).

In addition to body mass index (BMI) values, the study also considered various demographic factors, including social data and risk factors related to anesthesia and general outcome. This encompassed variables such as education level, employment status, and housing situation, as well as factors like the ASA score, smoking habits, and alcohol consumption.

The ASA score, which stands for the American Society of Anesthesiologists physical status classification system, is widely utilized in anesthesiology clinics to assess the overall health status of patients before surgery. This classification system divides patients into six severity levels: ASA 1 (indicating a healthy individual), ASA 2 (representing mild systemic disease), ASA 3 (indicating severe systemic disease), ASA 4 (representing severe systemic disease posing a constant threat to life), ASA 5 (indicating a moribund individual not expected to survive without the operation), and ASA 6 (representing a declared brain-dead individual undergoing organ removal for donation purposes). [116]

The distribution of ASA scores within the entire cohort was as follows: ASA 1 (n=3; 6%), ASA 2 (n=21; 42%), ASA 3 (n=24; 48%), and ASA 4 (n=2; 4%). Similarly, within the high-risk group, the distribution of ASA scores was as follows: ASA 1 (n=1; 5%), ASA 2 (n=8; 40%), ASA 3 (n=10; 50%), and ASA 4 (n=1; 5%). In the

low-risk group, the distribution of ASA scores was as follows: ASA 1 (n=2; 6.7%), ASA 2 (n=13; 43.3%), ASA 3 (n=14; 46.7%), and ASA 4 (n=1; 3.3%). (see Figure 18)

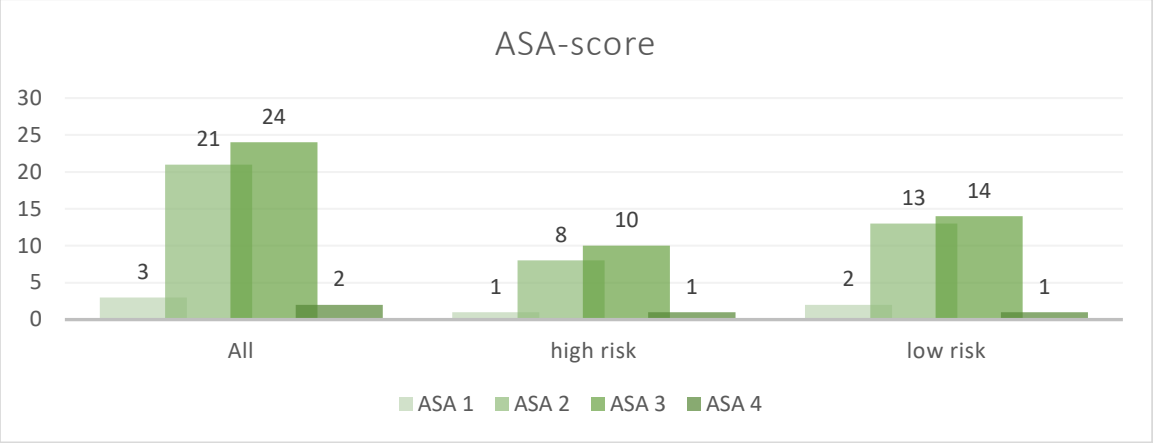

Figure 18: Classification of patients according to ASA.

To examine the educational backgrounds of the patients, they were categorized based on their level of education. The categories included mandatory school (equivalent to 9 years of education), vocational school (9 years of education plus 2-4 years of apprenticeship), high school (12 years of education), and bachelor's degree or higher (15+ years of education).

Figure 19 presents the distribution of patients across these education categories, with the respective bars indicating the number of patients (n=patient). The mode, or the most frequently occurring category, for the entire patient cohort is high school, which accounts for 20 patients. Within the high-risk group, the mode is vocational school, with eight patients falling into this category. Similarly, within the low-risk group, the mode is also high school, with 14 patients. It is important to note that a total of six patients (one in the high-risk group and five in the low-risk group) did not provide information regarding their education level.

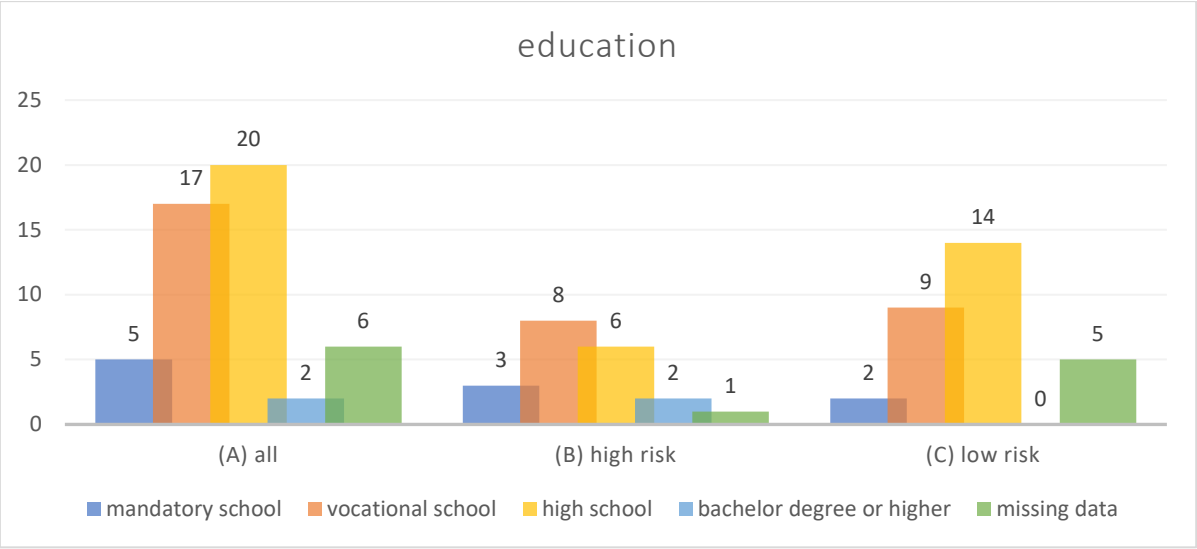

Figure 19: Demographic description of education level in the patient collective in general (A), for the high risk group (B), and the low risk group (C).

Patients self-reported their alcohol consumption habits on a scale ranging from zero to four. No further differentiation was made regarding the quantity consumed per instance. The mode category, observed in both the high-risk and low-risk groups, as well as among all the patients, was "never" (total of 19 patients, 9 in the high-risk group and 10 in the low-risk group) (see Figure 20).

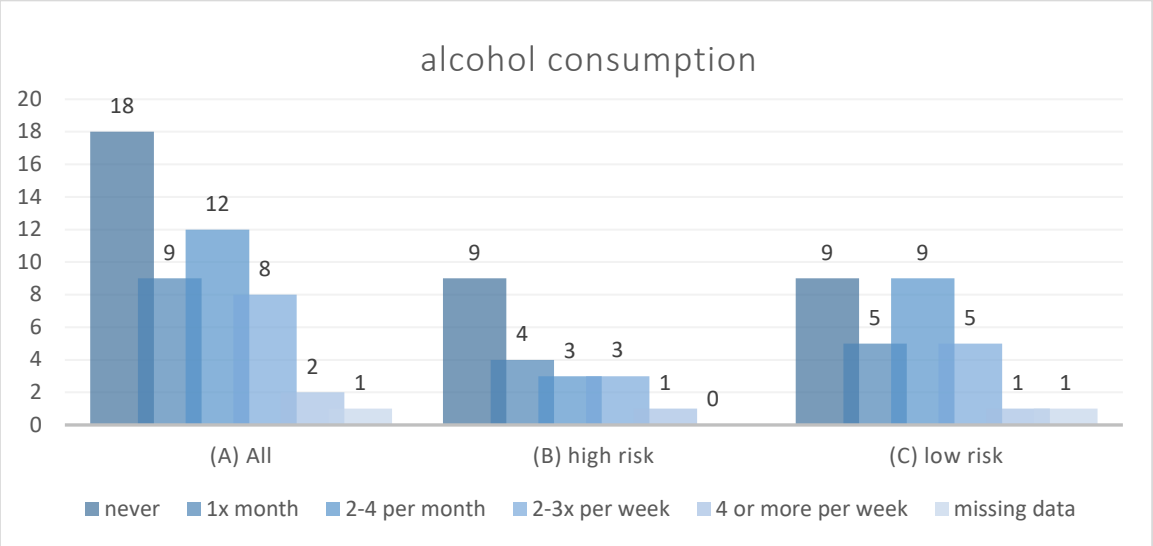

Figure 20: Demographic description of drinking habits in the patient collective in general (A), for the high risk group (B), and the low risk group (C) per week.

They also self-reported their smoking habits on a scale ranging from zero to three. The non-smoker category was the most frequently observed mode in both groups,

as well as among all the patients included in the study. Specifically, there were a total of 43 non-smokers, with 16 in the high-risk group and 27 in the low-risk group (see Figure 21).

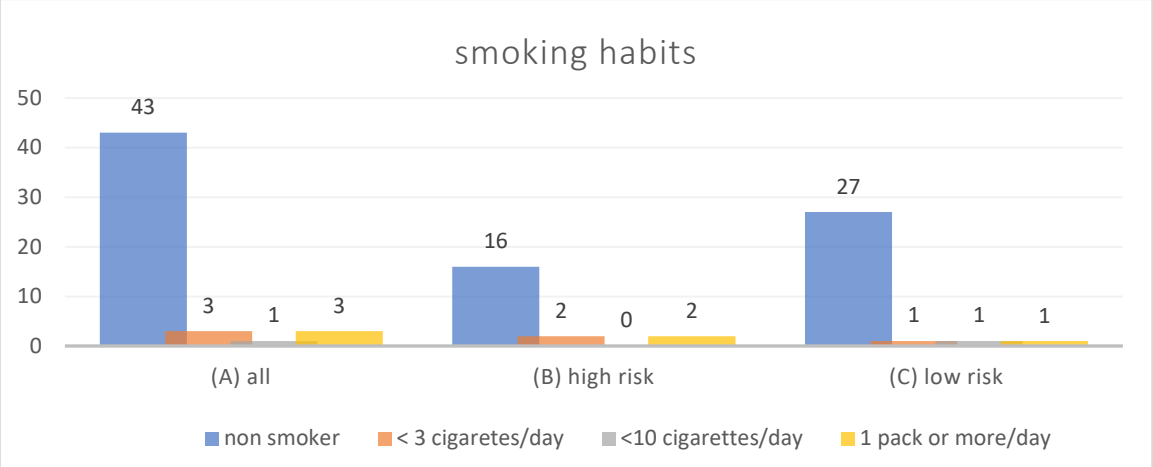

Figure 21: Demographic description of smoking habits in the patient collective in general (A), for the high risk group (B), and the low risk group (C) per day.

We conducted a preoperative analysis to compare the two groups by utilizing mean values and standard deviation (SD). Additionally, Student's T-test was employed to assess the differences between connected and independent samples. Significant disparities were identified in HADS depression (t (48) = -2.791, p = 0.008), HADS Anxiety (t (48) = -2.131, p = .038), and HADS total (t (48) = -2.614, p = .012) scores (see Table 8).

	N	Mean	SD	p-value
Age (years)				0.719
Low risk	30	66.767	9.5038	
High risk	20	67.800	10.4660	
BMI (weight/(height)^2				0.056
Low risk	24	33.180	6.1141	
High risk	16	29.695	4.2881	
NRS maximum today				0.188
Low risk	30	6.033	2.1891	
High risk	20	6.850	2.0072	
NRS rest				0.625
Low risk	30	2.133	2.0297	
High risk	20	2.450	2.5021	

NRS activity				0.867
Low risk	30	4.733	2.4344	
High risk	20	4.850	2.3458	
HADS depression				0.008**
Low risk	30	2.433	2.8610	
High risk	20	4.950	3.4864	
HADS Anxiety				0.038*
Low risk	30	5.667	3.9508	
High risk	20	8.200	4.3601	
HADS total				0.012*
Low risk	30	8.10	6.316	
High risk	20	13.15	7.228	
PCS				0.061
Low risk	30	11.067	10.3888	
High risk	20	16.850	10.5345	
KOOS pain				0.073
Low risk	30	16.367	6.5836	
High risk	20	19.750	6.1119	
KOOS symptoms				0.127
Low risk	30	11.433	4.3997	
High risk	20	13.650	5.6872	
KOOS activity				0.097
Low risk	30	29.733	11.9017	
High risk	20	35.600	12.1586	
KOOS functionality				0.198
Low risk	30	15.600	4.4691	
High risk	20	17.100	3.0933	
KOOS quality of life				0.232
Low risk	30	9.900	3.1770	
High risk	20	10.900	2.2919	
KOOS total				0.075
Low risk	30	83.033	26.0946	
High risk	20	97.000	27.2455	

*Table 8: Preoperative comparison of the baseline mean (SD) between the high risk and low risk group using t-test. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001*

Further, significant differences with a medium effect strength were found between the high risk and low risk group in the FSQ (Mann-Whitney-U test: U = 177.5, p = 0.014), the DN4 preoperative (Mann-Whitney-U test: U = 151, p = 0.005), after one week (Mann-Whitney-U test: U = 162, p = 0.005), and after six weeks (Mann-Whitney-U test: U = 198, p = 0.041) as well as significant differences with a strong effect in the HADS Score (Mann-Whitney-U test: U = 133.5, p < 0.001) (see Table 9)

	Fibromyalgie Score	HADS Score	DN4 pre-op	DN4 one day post-op	DN4 6 weeks post-op
Mann-Whitney-U	177.500	133.500	151.000	162.000	198.000
Wilcoxon-W	642.500	598.500	616.000	627.000	663.000
Z	-2.453	-3.551	-3.026	-2.789	-2.044
asymptomatic significance (2-sided)	0.014*	0.000***	0.002**	0.005**	0.041*

*Table 9: Mann-Whitney-U test. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001*

Comparing gender distribution between the high risk and the low risk group, a significant difference (sqared chi (df = 1, n = 50) = 4.58, p = 0.032) was presented (see Table 10).

	Value	Df	p
Sex	4.58	1	0.032*
ASA	.198	3	0.978
Smoking	.901	1	0.342
Allodynia	0.066	1	0.797

*Table 10: Pearson`s chi-squared-test, *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001*

Other than that, no significant differences in the preoperative comparison between the high-risk and low-risk group were found.

3.1 Analysis of Variance (ANOVA)

The SF36 questionnaire was assessed individually across each dimension, as detailed in the PROMs chapter. Preoperative, three-month, and six-month measurements were taken for mean and standard deviation. The detailed results of the repeated-measures analysis of variance for all subgroups are listed in table 10 and 11. We found significant differences in four subgroups of the SF36. In the subgroup of physical functioning, the effect size was found to be strong ($F(2,72) = 21.447$, $p < 0.001$, $\eta p2 = 0.373$, $n = 38$). Pairwise comparisons with Bonferroni correction indicated significantly higher scores after three months compared to the preoperative period ($p < 0.001$), as well as after six months compared to three months ($p = 0.049$).

The effect size in subgroup Role physical was strong ($F(2,78) = 12.964$, $p < 0.001$, $\eta p2 = 0.249$, $n = 41$). Bonferroni-corrected pairwise comparisons show significantly higher results after 3 months in comparison to preoperative ($p < 0.031$) as well as after 6 months in comparison to after 3 months ($p = 0.028$).

The effect size in subgroup energy/fatigue was medium ($F(1.76,68.76) = 5.28$, $p = 0.01$, $\eta p2 = 0{,}119$, $n = 41$). Bonferroni-corrected pairwise comparisons show significantly higher results after 3 months in comparison to preoperative ($p < 0.031$) but no significant difference after 6 months in comparison to after 3 months ($p = 1$).

The effect size in subgroup pain was strong ($F(1.77,68.88) = 30.5$, $p < 0.001$, $\eta p2 = 0{,}439$, $n = 41$). Bonferroni-corrected pairwise comparisons show significant higher results after 3 months in comparison to preoperative ($p < 0.001$) but no differences after 6 months in comparison to after 3 months ($p = 1$).

There was no significant interaction effect between the high risk and low risk group found in any subgroup.

	p-value within-subject effects	ηp^2 within-subject effects	p-value interaction effect[a]	ηp^2 interaction effect[a]
Physical functioning	< 0.001***	0.373	0.076	0.071
Role physical	< 0.001***	0.249	0.796	0.006
Role emotional	0.294	0.032	0.23	0.006
Energy/fatigue	0.01**	0.119	0.11	0.057
Emotional well-being	0.24	0.036	0.115	0.054
Social functioning	0.419	0.019	0.208	0.041
Pain	< 0.001***	0.439	0.62	0.011
General health	0.102	0.057	0.707	0.009

*Table 11: Within-subject effects in subgroups of SF36. [a]interaction effect between high risk and low risk group. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001*

	Mean (SD) preoperative	Mean (SD) 3 months	Mean (SD) 6 months	p-value pre vs. 3 months	p-value pre vs. 6 months	p-value 3 vs. 6 months
Physical functioning	40.848 (25.4)	57.836 (21.378)	66.447 (18.377)	< 0.001***	< 0.001***	0.049*
Role physical	23.415 (30.952)	41.463 (32.677)	56.707 (37.091)	0.031*	< 0.001***	0.028*
Role emotional	63.333 (42.57)	73.333 (37.893)	72.5 (37.658)	0.513	0.641	1
Energy/fatigue	51.829 (22.714)	60.732 (17.123)	60.854 (19.491)	0.031*	0.052	1
Emotional well-being	72.195 (20.532)	76 (16.613)	74.244 (19.122)	0.302	0.807	1
Social functioning	81.40 (58.10)	88.11 (14.24)	87.2 (18.43)	1	1	1
Pain	35.55 (20.79)	63.84 (17.29)	65.98 (19.97)	< 0.001***	< 0.001***	1
General health	62.42 (18.35)	68.11 (17.67)	65.12 (19.45)	0.117	0.778	0.923

*Table 12: Bonferroni-corrected pairwise comparisons in subgroups of SF36. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001*

Figure 22 provides a visual representation of the mean and SD for the SF36 subgroups throughout the study, including the preoperative assessment, the 3-month, and the 6-month follow-up. Values in the high-risk group generally trended lower across most subgroups. However, these differences were not statistically significant. For precise numerical values, refer to Table 13.

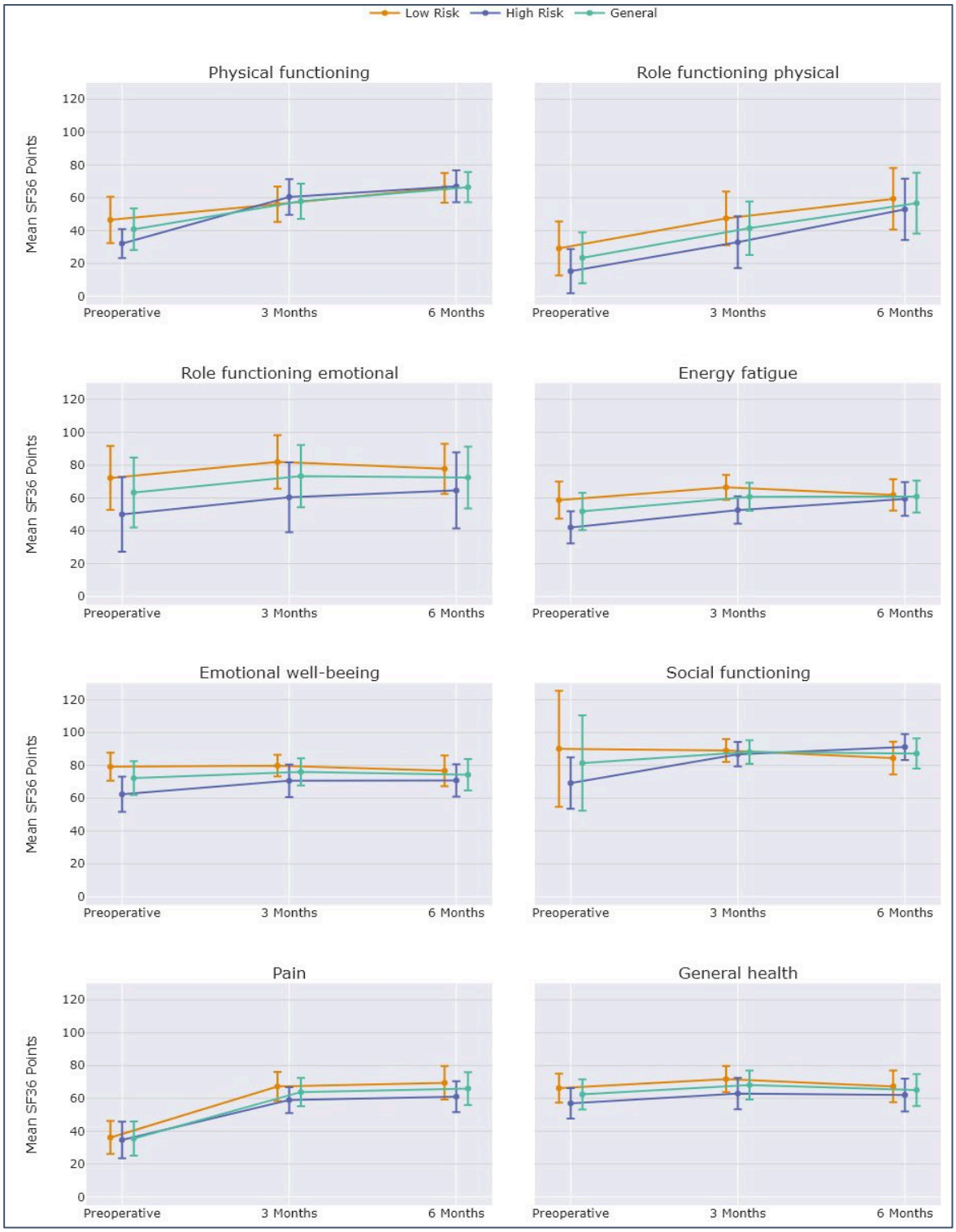

Figure 22: This graph compares the measured mean values in subgroups of the SF36 preoperatively, after three months, and after 6 months. For a better overview, the individual groups are presented slightly offset from each other and SD scaled by a factor of 0.5. Exact values can be looked up in table 12.

Time	Low-risk		High risk		Gesamt	
	Mean	SD	Mean	SD	Mean	SD
Physical functioning						
Preoperative	46.522	28.302	32.148	17.711	40.848	25.41
3 months	56.087	21.477	60.519	21.687	57.836	21.378
6 months	66.087	18.025	67.000	19.530	66.447	18.377
Role functioning/physical						
Preoperative	29.167	32.826	15.294	26.953	23.415	30.952
3 months	47.5	32.737	32.941	31.576	41.463	32.677
6 months	59.375	37.455	52.941	37.377	56.707	37.091
Role functioning/emotional						
Preoperative	72.222	38.906	50	45.542	63.333	42.57
3 months	81.944	32.57	60.417	42.546	73.333	37.893
6 months	77.778	30.561	64.583	46.298	72.5	37.658
Energy/fatigue						
Preoperative	58.750	22.614	42.059	19.530	51.829	22.714
3 months	66.458	15.286	52.647	16.688	60.732	17.123
6 months	61.875	18.986	59.412	20.682	60.854	19.491
Emotional well-being						
Preoperative	79.167	17.092	62.353	21.404	72.195	20.532
3 months	79.833	13.107	70.588	19.745	76	16.613
6 months	76.667	18.786	70.824	19.635	74.244	19.122
Social functioning						
Preoperative	90.104	70.709	69.118	31.287	81.402	58.103
3 months	89.063	13.945	86.765	14.968	88.11	14.239
6 months	84.375	19.935	91.176	15.79	87.195	18.432
Pain						
Preoperative	36.146	20.108	34.706	22.324	35.549	20.793
3 months	67.292	17.753	58.971	15.862	63.841	17.294
6 months	69.479	20.336	61.029	18.917	65.976	19.968
General health						
Preoperative	66.25	17.647	57	18.453	62.415	18.345
3 months	71.771	16.024	62.941	19.044	68.11	17.667
6 months	67.292	19.223	62.059	19.926	65.122	19.445

Table 13: Results of mean (SD) for each subgroup of the SF36 preoperative, after three months, and after 6 months.

Table 13 and 14 present the results of the repeated-measures analysis of variance of the WOMAC index, indicating a significant difference in WOMAC total scores, as well as in all subgroups.

The effect size in the WOMAC total was strong ($F(2,96) = 48.523$, $p < 0.001$, $\eta p2 = 0.505$, $n = 50$). Bonferroni-corrected pairwise comparisons show significantly higher results after 3 months in comparison to preoperative ($p < 0.001$) but no significant difference after 6 months in comparison to after 3 months ($p = 1$).

The effect size in subgroup pain was strong ($F(2,96) = 64.126$, $p < 0.001$, $\eta p2 = 0.572$, $n = 50$). Bonferroni-corrected pairwise comparisons show significantly higher results after 3 months in comparison to preoperative ($p < 0.001$) but no significant difference after 6 months in comparison to after 3 months ($p = 0.869$).

The effect size in subgroup stiffness was strong ($F(2,96) = 24.72$, $p < 0.001$, $\eta p2 = 0.34$, $n = 50$). Bonferroni-corrected pairwise comparisons show significantly higher results after 3 months in comparison to preoperative ($p < 0.001$) but no significant difference after 6 months in comparison to after 3 months ($p = 0.1$).

The effect size in subgroup activity was strong ($F(2,96) = 41.205$, $p < 0.001$, $\eta p2 = 0.46$, $n = 50$). Bonferroni-corrected pairwise comparisons show significantly higher results after 3 months in comparison to preoperative ($p < 0.001$) but no significant difference after 6 months in comparison to after 3 months ($p = 1$).

There was a significant interaction effect between the high risk and low risk groups found in subgroups pain ($p = 0.027$) and stiffness ($P = < 0.001$) with both subgroups having a better outcome in the high risk group over the low risk group.

WOMAC subgroups	p-value within-subject effects	ηp^2 within-subject effects	p-value interaction effect[a]	ηp^2 interaction effect[a]
Pain	< 0.001***	0.572	0.027*	0.08
Stiffness	< 0.001***	0.34	< 0.001***	0.169
Activity	< 0.001***	0.46	0.587	0.01
Total	< 0.001***	0.505	0.522	0.013

*Table 14: Within-subject effects in subgroups of WOMAC. [a]interaction effect between high risk and low risk group. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001*

WOMAC subgroups	Mean (SD) preoperative	Mean (SD) 3 months	Mean (SD) 6 months	p-value preop vs. 3 months	p-value preop vs. 6 months	p-value 3 vs. 6 months
Pain	40.36 (19.347)	12.28 (10.736)	14.44 (15.023)	< 0.001***	< 0.001***	0.869
Stiffness	43.9 (26.903)	21.7 (19.499)	23.9 (19.956)	< 0.001***	< 0.001***	1
Activity	40.904 (20.144)	16.074 (15.256)	16.732 (13.985)	< 0.001***	< 0.001***	1
Total	41.052 (18.852)	15.766 (13.191)	16.836 (13.432)	< 0.001***	< 0.001***	1

*Table 15: Bonferroni-corrected pairwise comparisons in subgroups of WOMAC. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001*

Figure 23 illustrates the mean values and SD for the WOMAC subgroups throughout the study, including the preoperative assessment, the 3-month follow-up, and the 6-month follow-up. Preoperative values exhibited lower scores across all subgroups in the low-risk group. However, after 3 months and 6 months, values in the high-risk group consistently displayed lower scores in all subgroups with significant interaction effects presented in subgroups pain (p = 0.027) and stiffness (p < 0.001). For a detailed numerical values, refer to Table 16.

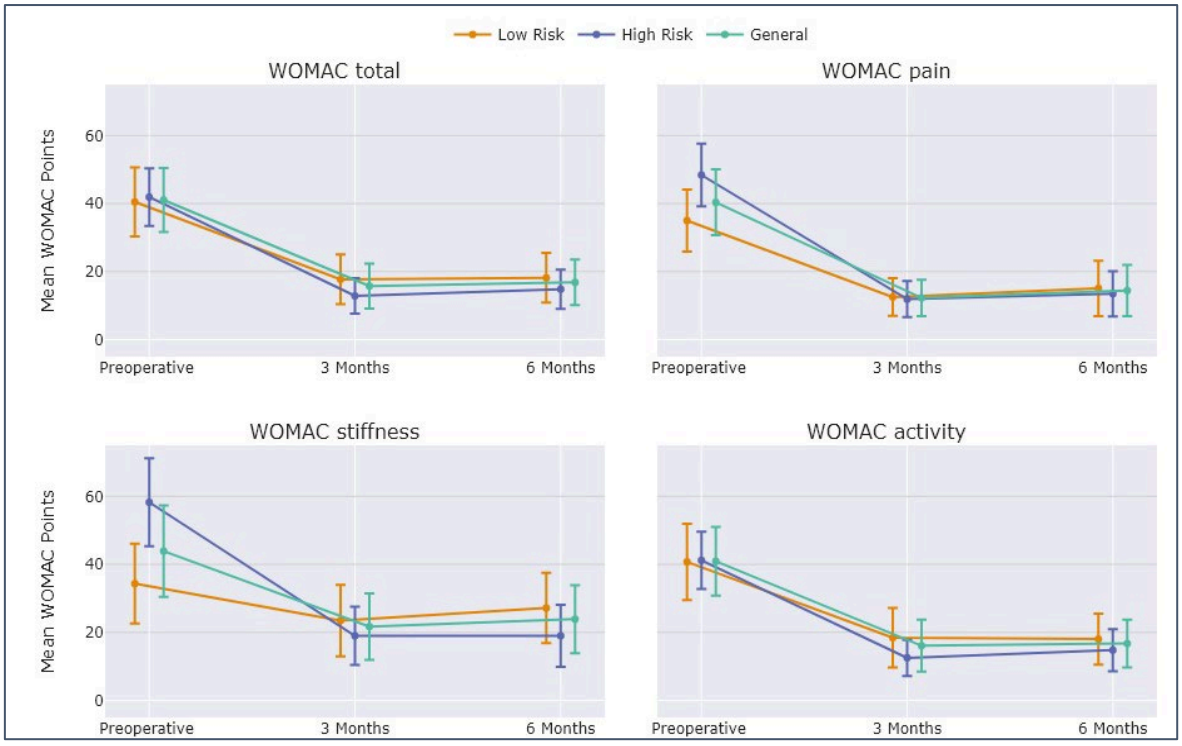

Figure 23: This graph compares the measured mean values in subgroups of the WOMAC score preoperatively, after three months, and after 6 months. For a better overview, the individual groups are presented slightly offset from each other and SD is scaled by a factor of 0.5. Exact values can be looked up in Table 15.

Time	Low-risk		High risk		Gesamt	
	Mean	SD	Mean	SD	Mean	SD
WOMAC total						
Preoperative	40.487	20.283	41.9	16.95	41.052	18.852
3 months	17.703	14.607	12.86	10.405	15.766	13.191
6 months	18.17	14.604	14.835	11.522	16.836	13.432
WOMAC pain						
Preoperative	35	18.276	48.4	18.497	40.36	19.347
3 months	12.533	10.991	11.9	10.612	12.28	10.736
6 months	15.067	16.271	13.5	13.28	14.44	15.023
WOMAC stiffness						
Preoperative	34.333	23.442	58.25	25.817	43.9	26.903
3 months	23.5	21.015	19	17.137	21.7	19.499
6 months	27.167	20.665	19	18.253	23.9	19.956
WOMAC activity						
Preoperative	40.723	22.379	41.175	16.79	40.904	20.144
3 months	18.437	17.471	12.530	10.6	16.074	15.256
6 months	18.037	14.998	14.775	12.425	16.732	13.985

Table 16: Results of mean (SD) for each subgroup of the WOMAC preoperative, after three months, and after 6 months.

The effect size in NRS maximum was strong ($F(2,78) = 44.026$, $p < 0.001$, $\eta p2 = 0.530$, $n = 41$) (see table 16). Bonferroni-corrected pairwise comparisons show significantly higher results after 3 months in comparison to preoperative ($p < 0.001$) but no significant difference after 6 months in comparison to after 3 months ($p = 1$) (see Table 17).

The effect size in NRS activity was strong ($F(2,78) = 17.359$, $p < 0.001$, $\eta p2 = 0.308$, $n = 41$) (see table 16). Bonferroni-corrected pairwise comparisons show significantly higher results after 3 months in comparison to preoperative ($p < 0.001$) but no significant difference after 6 months in comparison to after 3 months ($p = 1$) (see Table 17).

The effect size in NRS rest was strong ($F(2,78) = 8.782$, $p = 0.001$, $\eta p2 = 0.184$, $n = 41$) (see table 16). Bonferroni-corrected pairwise comparisons show significantly higher results after 3 months in comparison to preoperative ($p < 0.032$) but no significant difference after 6 months in comparison to after 3 months ($p = 0.683$) (see table 17). There was no significant interaction effect between the high risk and low risk groups found in any subgroup (see Table 17).

NRS subgroups	p-value within-subject effects	ηp^2 within-subject effects	p-value interaction effect[a]	ηp^2 interaction effect[a]
Maximum	< 0.001***	0.530	0.592	0.013
Rest	= 0.001**	0.184	0.451	0.019
Activity	< 0.001***	0.308	0.744	0.007

*Table 17: Within-subject effects in subgroups of NRS. [a]interaction effect between high risk and low risk groups. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001*

NRS subgroups	Mean (SD) preoperative	Mean (SD) 3 months	Mean (SD) 6 months	p-value pre-op vs. 3 months	p-value pre-op vs. 6 months	p-value 3 vs. 6 months
Maximum	6.488 (2.026)	2.951 (2.121)	2.805 (2.522)	< 0.001***	< 0.001***	1
Rest	2.244 (2.267)	1.049 (1.264)	0.805 (1.504)	0.032*	0.002**	0.683
Activity	4.659 (2.352)	2.439 (2.013)	2.414 (1.9618)	< 0.001***	< 0.001***	1

*Table 18: Bonferroni-corrected pairwise comparisons in subgroups of NRS. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001*

4 Discussion

Being the most prevalent disabling joint disorder, Osteoarthritis of the knee represents a substantial challenge for public health, leading to notable implications for affected individuals, health care systems, and imposing substantial socioeconomic costs. [132]

Despite a well-established, stepwise treatment regimen encompassing physical therapy, pharmacological interventions, and surgical approaches, the present state of knowledge indicates that a definitive cure for Osteoarthritis remains elusive. The current focus revolves around impeding disease progression to the greatest extent possible, primarily through conservative interventions, while reserving surgical measures for cases where non-surgical options have been exhausted, aiming to alleviate symptoms. However, despite achieving satisfactory outcomes in some instances, it is noteworthy that the proportion of dissatisfied patients is notably higher in total knee arthroplasty (TKA) compared to joint replacement interventions targeting other joints. Of particular concern is the occurrence of chronic postsurgical pain (CPSP), which presents a significant challenge, affecting approximately 15% of patients following TKA. [1]

It is postulated that the primary etiological factor contributing to the development of CPSP is the presence of an underlying neuropathic pain component resulting from both peripheral and central sensitization mechanisms. These processes lead to alterations in pain pathways and diminish the effectiveness of commonly used analgesic interventions. In these patients, personalized therapy utilizing co-analgesics becomes imperative, underscoring the significance of prompt recognition and appropriate treatment to optimize overall patient outcomes and satisfaction. [2] According to existing literature, a correlation has been observed between demographic factors, including female gender and young age, psychological factors such as depression, excessive anxiety, and worries, pre-existing chronic pain, as well as prolonged use of analgesics, and a deterioration in the outcome. [3]

The documentation of these factors presents an opportunity to prospectively identify patients at a heightened risk of developing chronic postsurgical pain (CPSP), enabling early initiation of appropriate therapeutic interventions,

particularly in cases involving neuropathic pain. A total of 50 patients participated in the study to investigate the impact of these risk factors. They underwent a predetermined screening protocol consisting of various patient-reported outcome measures (PROMs), clinical examinations, and an assessment of their medical history. The obtained data were subsequently reviewed by two experienced senior physicians from our clinic´s Department of Anesthesiology. As a result, 20 patients were identified as having an increased risk of developing CPSP based on the identified risk factors. The remaining 30 patients did not exhibit characteristics associated with an elevated risk and were designated as the low-risk control group.

To assess whether the classification of patients into distinct groups resulted in significant differences that could potentially impose limitations on further data analysis, the initial preoperative values were compared using a t-test. The comparison of patient cohorts revealed noteworthy disparities in various measures, including the Hospital Anxiety and Depression Scale (HADS) (specifically the HADS depression subgroup ($p = 0.008$), HADS anxiety subgroup ($p = 0.038$), and HADS total ($p = 0.012$)), as well as the Mann-Whitney-U test results ($p < 0.001$), the FSQ ($p = 0.014$), and the DN4 questionnaire ($p = 0.005$). Given that the grouping of patients was partially based on the outcomes of these patient-reported outcome measures (PROMs), the observed differences were anticipated and should not be regarded as limiting factors affecting the subsequent analysis of the data.

In the classification process, preoperative values in the Pain Catastrophizing Scale (PCS) were also considered. The results in the high-risk group demonstrated slightly higher values compared to the low-risk group, although this difference did not reach statistical significance ($p = 0.061$). Pain catastrophizing, as a psychological factor, holds significance and has been reported in the literature as a negative predictor for the occurrence of postoperative pain following total knee arthroplasty (TKA) [133–135] However, a study conducted by Hovik et al. examined the effects of preoperative pain catastrophizing on postoperative pain after one year and found no associations, challenging the evidence supporting the role of PCS in this particular context. [136]

Furthermore, it should be noted that the presence of risk factors for neuropathic pain correlates with higher numbers in pain levels in general as well as worse results in both investigated knee specific outcome scores (KOOS, WOMAC) preoperatively, which was partly to be expected, as the presence of pain is included in some PROMs as well as in the knee-specific scores, and their results are reduced at presence of higher pain levels.

In terms of demographic factors, the only significant differences were found in gender distribution. The proportion of women in the high risk group (80%) was significantly higher than in the low risk group (50%) ($p = 0.032$). This can also most likely be explained by the factors on which the classification is based. Controversial opinions regarding the gender distribution of neuropathic pain are described in the literature, but in general, women tend to be more prone to pain as well as depression, both being symptoms which are decisive in the PROMs used in the classification of the groups. [137–140] A meta-analysis done by Abate et al., analysed the presence of depression in a total of 19639 participants, concluding that men are 63% less likely to develop depression than women. [140] Also, women generally have a higher probability of developing knee osteoarthritis and due to the manageable population of the study, the variances are rather broad and may have contributed to these findings even more. [14]

In order to quantify the hypothesis that the risk of developing CPSP can be predicted, we placed particular emphasis on assessing the subjective pain perception of the patients throughout the study. To accomplish this, we employed ANOVA to investigate changes in outcomes across various measurement time points within each group, as well as differences between the two groups, thus assessing the impact of classification on the results.

Analyses were performed on the Numeric rating scale, the SF36, and the WOMAC score, with particular focus on the subgroups “pain”. Our findings revealed significant improvements of the preoperative baseline scores after three months in all NRS subgroups (NRS maximum: $p < 0.001$, NRS rest: $p = 0.032$, NRS activity: $p < 0.0019$) and the WOMAC subgroups (WOMAC pain: $p < 0.001$, WOMAC stiffness: $p < 0.001$, WOMAC activity $p < 0.001$, WOMAC total: $p < 0.001$). In the SF36, we found improvement in subgroups physical functioning ($p < 0.001$), role

physical ($p = 0.031$), energy/fatigue ($p = 0.031$), and pain ($p < 0.001$), while there was no significant difference in subgroups role emotional ($p = 0.513$) emotional well-being ($p = 0.302$), social functioning ($p = 1$), and general health ($p = 0.117$).

Two subgroups of the SF36 (physical functioning: $p = 0.049$, and role physical: $p = 0.028$) showed further significant improvement after six months compared to the results after three months as well. Other subgroups in the SF36 and all subgroups of the NRS and the WOMAC score showed no further significant differences. These results indicate a strong positive effect of the TKA performed in our population across both groups and are consistent with findings in the literature. [141, 142]

Two subgroups of the WOMAC (subgroup pain: $p = 0.027$, and subgroup stiffness: $p < 0.001$) showed a significant interaction effect between the two groups over the course of the study. In both subgroups, the values in the high risk group were lower than those in the low risk group. These results do not correlate with the set hypothesis and most prevailing opinions in the literature, implementing a worse outcome in the high risk group. [3, 142] In contrast to this, Lee et al. investigated the effects of preoperative neuropathic pain, pain at night, or depressive disorder in TKAs and concluded that patients with these conditions reported poorer functional and quality of life scores preoperatively, but the adverse effects disappeared and had no impact on the outcome after one year. [143]

Another important reference point in the study was to investigate the validity of the DN4 questionnaire as a tool for the identification of possible neuropathic pain and further as a predictor for CPSP. This was done by raising data preoperative, on the first day postoperative, and six weeks postoperative and comparing the results of our groups using the Mann-Whitney-U test. Our results show significantly higher values in the high risk group at all measurement points with a small reduction in significance at the latter measure point (preoperative: $p = 0.002$, first day postoperative: $p = 0.005$, six weeks postoperative: $p = 0.041$). These findings show that the possible neuropathic pain component in our high risk group was present preoperatively as well as in the early follow-ups, which is consistent to some point with the findings of higher pain values and lower clinical and life quality scores in this group. The findings of Beloeil et al., who described that acute

neuropathic pain in the first few days postoperatively significantly increases the risk of developing CPSP, however could not be reproduced in our study, since there was no significant difference in the endpoints described above. [4] Hasegawa et al. also concluded that there might be an association between preoperative presence of possible neuropathic pain and the development of CPSP. [144]

On the other hand, Fitzsimmons et al. had a similar approach to ours and came to the conclusion that suspected neuropathic pain leads to higher levels of pain, catastrophizing, and depression, but may have a limited prognostic value for the outcome of TKA after 6 months. [145]

Limitations

Our study had several limitations that should be acknowledged. Firstly, the relatively small sample size of 50 patients, resulting from a predefined recruitment schedule, limits the level of evidence and generalizability of our findings to larger populations.

The impact of outpatient follow-up, including the utilization of adjunctive therapies such as physical therapy, massage, lymphatic drainage, cardiovascular exercises, or weight training, plays an important role for the overall outcome after TKA but was not assessed in our study. [146]

Additionally, we did not investigate genetic factors that could play a role in the development of CPSP. Certain genetic polymorphisms have been associated with an increased risk of developing chronic pain after surgery. These genetic factors can affect pain sensitivity, inflammation, and the body's response to analgesic medications.[147–149]

A potential limitation of our study is that the DN4 questionnaire was administered only during the perioperative phase up to six weeks after the surgery, based on the study by Beloeil et al. Collecting data from the DN4 questionnaire at additional time points, such as 3 months and 6 months, would have provided more meaningful insights into the correlation between the neuropathic pain component and the development of chronic postsurgical pain (CPSP). This could have helped determine if there was a similar convergence of the two groups as observed in other assessments.

Furthermore, it should be acknowledged that the involvement of multiple surgeons and the utilization of different implant types in the study could potentially introduce variability and influence the outcomes. However, it is important to recognize that these factors are inherent to the everyday clinical practice in a diverse clinic setting. While it introduces certain limitations to the study, it also provides valuable insights into the effectiveness and outcomes of TKA under routine clinical conditions.

The last aspect that should be considered as a limitation is the reliance on individual interpretation and the experience of senior doctors for the final decision on group division, despite the initial classification being based on standardized patient-reported outcome measures (PROMs). While the use of PROMs is common in everyday clinical practice as supportive tools for diagnosis and decision-making, the subjectivity introduced by individual interpretation may have affected the validity of these standardized measures in this study.

Future research could benefit from implementing a more standardized and objective approach to group division, such as utilizing predefined cut-off scores or criteria based on the PROMs, in order to enhance the reliability and reproducibility of the findings.

Conclusion

In conclusion, our study found that patients identified as having a higher risk for developing CPSP based on our screening protocol experienced higher levels of pain and worse clinical outcomes and health-related quality of life preoperatively and in the early postoperative period. However, over the course of the study, the differences between the high-risk and low-risk groups diminished, and in some parameters, like the subgroups pain and stiffness of the WOMAC, the high-risk group even showed significantly lower values compared to the low-risk group at the final 6-month follow-up. Therefore, our hypothesis that screening procedures can accurately identify individuals at increased risk for developing CPSP could not be confirmed.

Nevertheless, the results did indicate a correlation between preoperative neuropathic pain and other risk factors with a worsened early postoperative course. Despite these conditions, total knee arthroplasty (TKA) still provided

satisfactory outcomes for the patients. Further analysis of our dataset and continued research in this field are necessary to explore if better indicators for predicting CPSP can be identified.

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