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DISSERTATION

Comparative Effectiveness of Ayurveda Treatment and Conventional Care in Knee Osteoarthritis – a Randomized Controlled Trial

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Foreword

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List of Abbreviations

Abbreviation	Description
AE	Adverse Events
BMI	Body Mass Index
CAM	Complementary and Alternative Medicine
CI	Confidence Interval
CIM	Complementary and Integrative Medicine
COX	Cyclooxygenase
CRF	Case Report Forms
Health Survey	Health-related quality of life
MCS	Mental Component Score
NRS	Numeric Rating Scales
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
PCS	Physical Component Score
PDI	Pain Disability Index
POMS	Profile of Mood States
RCT	Randomized Controlled Trial
SAE	Serious Adverse Events
SMD	Standardized Mean Difference
SOP	Standard Operating Procedures
SES	Pain Experience Scale
SF-36	Short Form-36

WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Abstrakt

Arthrose ist eine Erkrankung von globaler Relevanz. Weltweit leiden über 250 Mio. Menschen an Gonarthrose [Michaud 2006; OARSI 2016; Bitton 2009; Abramson 2009]. Trotz Fortschritten in der konservativen Gonarthroseversorgung gibt es Patienten, die im Anschluss der Therapie weiterhin mit Einschränkungen leben müssen. Daraus resultiert ein Bedarf an wirkungsvollen, zusätzlichen Behandlungsmethoden [McAlindon 2014; Hochberg 2012; Griffin 1991]. In Südasien ist die traditionelle ayurvedische Medizin eine weitverbreitete Behandlungsform bei Gonarthrose. Im Ayurveda kommen individualisierte Behandlungen mit multimodalem Konzept unter Miteinbeziehung von Manual- und Ernährungstherapie, Phytotherapie, Lebensstil-Beratung sowie Yoga-Übungen zum Einsatz [Tuffs 2002]. Jedoch liegen bislang noch keine klinischen Studien zur Behandlung von Gonarthrose mit Ayurveda durch einen solchen Ansatz vor [Hegana 2016].

Ziel dieser Arbeit war es, die klinische Wirksamkeit eines ayurvedischen Therapieverfahrens am Beispiel der Gonarthrose zu überprüfen. Hierbei wurde ein Vergleich der beiden Behandlungsmethoden Ayurveda und konventionelle Therapie bei Gonarthrose vorgenommen. Hierzu wurden Probanden mit diagnostizierter Gonarthrose gemäß der ACR-Kriterien (American College of Rheumatology) in eine "multizentrische, randomisierte, kontrollierte klinische Studie eingeschlossen." Von 151 Patienten erhielten 77 ausschließlich eine Ayurveda-Behandlung und 74 eine konventionelle Behandlung. Dabei erhielten die Patienten über einen Behandlungszeitraum von 12 Wochen jeweils 15 Therapiesitzungen. Der Primärzielparameter stellte der Western Ontario und McMaster University Osteoarthritis Index (WOMAC Index) in der validierten deutschen Version dar. Die Änderungen des WOMAC Index wurden über einen Zeitraum von 12 Wochen beobachtet. Zu den sekundären Zielparametern gehörten die WOMAC-Subskalen (Schmerz, Steifigkeit, Funktion); validierte Fragebögen für Schmerz, Schmerzerfahrung, Lebensqualität und Stimmung; numerische Ratingskalen für Schmerz und Schlafqualität sowie Bedarfsmedikationsgebrauch und Sicherheitsaspekte. [Kessler 2018]

Zusammenfassend lässt sich feststellen, dass die Änderungen im WOMAC Index zwischen Ausgangswerten und dem Ergebnis nach 12 Wochen in der Ayurveda Gruppe signifikant stärker ausgeprägt waren (Mittelwertdifferenz 61,0 [95 % CI 52,4; 69,6]) als

in der konventionellen Gruppe (32,0 [95 % CI 21,4;42,6]). Des Weiteren ließen sich signifikante Unterschiede zwischen den beiden Gruppen ($p < 0,001$) und der klinisch relevanten Effektgröße (Cohens d 0,68 [95 % CI 0,35; 1,01]) feststellen. Auch für viele sekundäre Zielparameter konnten ähnliche Tendenzen zu Gunsten des Ayurveda beobachtet werden. Darüber hinaus waren Effekte noch 3 und 9 Monaten nach der letzten Behandlung nachweisbar. Die Ergebnisse deuten darauf hin, dass die Behandlung der Gonarthrose mittels einer komplexen Ayurveda-Therapie im Vergleich zur komplexen konventionellen Therapie womöglich überlegen sein könnte. Jedoch sind zunächst weiterführende Studien erforderlich, um die Wirksamkeit zu belegen und um die Einflüsse der verschiedenen Behandlungskomponenten sowie die Einflüsse der nicht-spezifische Effekte weiter zu klären. [Kessler 2018]

Abstract

Osteoarthritis (OA) is of global relevance with up to 250 million people affected by knee OA [Michaud 2006; OARSI 2016; Bitton 2009; Abramson 2009]. Despite progress in conventional care, patients continue to be affected by disability, and there is a need for further treatment approaches [McAlindon 2014; Hochberg 2012; Griffin 1991]. In South Asia, Ayurveda is commonly used as a treatment approach in knee OA. Ayurveda uses individualized treatments with a multi-modal concept utilizing manual and nutritional therapy, herbal therapy, lifestyle counseling and yoga [Tuffs 2002]. No clinical trial evaluated Ayurveda treatment with such an approach for knee OA prior to this study [Lauche 2016].

The goal was to analyze clinical effectiveness of an Ayurvedic method by example of treatments on patients with knee OA. In this case, a comparison was made of the treatment methods Ayurveda and conventional therapy of knee OA. For this purpose, patients diagnosed with knee OA according to ACR (American College of Rheumatology) criteria were included in a "multicenter, randomized, controlled clinical trial". Of 151 enrolled patients, 77 received Ayurveda therapy and the remaining 74 were treated by conventional therapy. Every participant received 15 treatments during a period of 12 weeks. The primary outcome was the change on the Western Ontario and McMaster University Osteoarthritis (WOMAC) Index according to the validated German version after 12 weeks. Parameters for the secondary outcome consisted of WOMAC subscales (pain, stiffness, function); validated questionnaires for pain, pain experience, quality of life and mood; numeric rating scales for pain and sleep quality; rescue medication use and safety issues. [Kessler 2018]

In summary, the improvements shown in the WOMAC Index from baseline to 12 weeks were greater in the “Ayurveda group (mean difference 61.0 [95 % CI: 52.4;69.6]) than in the conventional group (32.0 [95 % CI: 21.4;42.6])”. Moreover, this result was underlined with a significant between-group “difference ($p<0.001$) and a clinically relevant effect size (Cohen’s d 0.68 [95 % CI:0.35;1.01])”. After 12 weeks of treatment, comparable effects in favor of Ayurveda were detected for a number of secondary outcomes. Furthermore, even 3 and 9 months after the last treatments therapy effects persisted. These findings imply that the treatment of knee OA with a complex Ayurvedic therapy might be superior to a complex conventional OA therapy.

However, additional studies are required to examine the extent of the effectiveness and to illuminate further the influence of diverse treatment factors and "non-specific effects". [Kessler 2018]

1. Preface

Osteoarthritis (OA) is a debilitating joint disease and is responsible for moderate to severe joint pain and functional limitations, adversely affecting the life quality of patients [Kotti 2014; Michaud 2006]. OA is of global relevance with up to 250 million people being affected by OA of the knee worldwide [Kotti 2014]. It is a tremendous economic global burden with annual healthcare costs exceeding $ 185 billion because of the effects of disability, comorbidity and the cost of treatments [Kotlarz 2009]. According to the German Federal Statistical Office, around $ 10.7 billion (€ 8.7 billion) was spent on medical treatment and care of OA in the year 2015 [StBA 2017]. Considering that 53 % of all OA patients are suffering from OA of the knee (male 53.4 %; female 53.0 %) [Fuchs 2013], costs of the order of about $ 3.6 billion (€ 2.9 billion) for OA of the knee are being issued every year in Germany.

Despite the developments in the scientific understanding of OA there are at present no curative therapies for OA [Abramson 2009]. To relieve symptoms, clinical guidelines recommend both non-pharmacological and pharmacological methods [McAlindon 2014; Hochberg 2012]. Unfortunately, pharmacological approaches may lead to serious adverse effects [Griffin 1991; Hernández-Díaz 2001]. Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the more common treatments for OA. They increase the risk of peptic ulcer bleeding and/or perforation, atrial fibrillation, chronic kidney disease or even death from cardiovascular disease [Lanza 2009; Liu 2014; Hsu 2015; Trelle 2011].

Hence many patients try treatments of Complementary and Alternative Medicine (CAM) with less or no side effects [Berman 2002; NCCIH 2008]. The use of CAM has been increasing worldwide. For example, currently 70 % of the population in Canada and 80 % in Germany have used CAM in their lifetime [PCAHC 2001; Tuffs 2002]. The National Health Interview Survey (NHIS) showed that 38 % of adults in the US use CAM. Particularly patients with chronic conditions often use CAM for self-care and disease management [Falci 2016]. There are also several CAM treatments for OA of the knee. A systematic study of Lauche et al. found a useful application of Cabbage Leaf Wraps to reduce pain of OA of the knee [Lauche 2016]. Furthermore, there are whole medical systems such as Traditional Chinese Medicine where studies of phytotherapy, Tai Qi or acupuncture showed an effective reduction of pain and improvement of the physical function of OA of the knee [Chen 2015; Wang C 2016; Karner 2013; Vas 2004].

Medical leech therapy is another method used to treat OA of the knee [Lauche 2014]. It is also one of the manifold therapies of Ayurveda which is used in South Asia as a broad system of medicine [Kessler 2012].

Ayurveda is regulated in India by an independent ministry (AYUSH) and recognized as Traditional Indian Medicine by the World Health Organization (WHO) [CCRAS 2015; WHO 2010]. In contrast to conventional western mainstream medicine, Ayurvedic concepts are based on individually tailored, constitution-based multimodal therapies including elements from manual therapy, nutritional therapy, botanical therapy, meditation and yoga, spiritual practices, cleansing measures, leech-application and lifestyle counseling [Sharma RK 2002; Upadhyaya 1993; Gupta 2009]. Ayurveda also provides complex treatments for OA, but to date there is no clinical study on OA with a multidimensional approach of Ayurveda as a whole medical system. A systematic review of 33 studies showed that most trials (91 %) evaluated herbal Ayurvedic preparations as single interventions [AAPNA 2007; Upadhyay 2010; Pathak-Gandhi 2016]. Furthermore, randomized controlled studies on Ayurveda focused only on structural Western diagnoses and disease cognition without consideration of the principles of the traditional Ayurvedic diagnostic approach [Bhat 2007; Chopra 2011].

Based on this, there is a need to evaluate Ayurveda as a whole medical system and complex treatment taking modern western and traditional Ayurvedic diagnostic aspects into account. Therefore, the aim of this study was to compare the effectiveness of a complex Ayurvedic treatment based on Ayurvedic diagnosis with complex conventional guideline care in patients with OA of the knee. [Kessler 2018]

2. Background

The aim of this chapter is to present the current state of knowledge of OA of the knee with the help of etymology, etiology, prevalence and incidence statistics, clinical presentation and current treatments.

2.1 Osteoarthritis

2.1.1 Etymology

The word osteoarthritis consists of the Greek roots “osteo” which means "of the bone", and “arthron”, meaning "joint" [Arya 2013]. While the Greek ending “-itis″ normally indicates an inflammation, currently, OA is classified as a non-inflammatory process. OA had been seen for a long time as an inflammation process, but already in 1925, the internist Herbert Assmann described it as a slowly progressing, degenerative process [Mayer 2009].

In contrast to OA, rheumatoid arthritis (RA) is an immune-mediated inflammatory disease characterized mainly by synovitis and joint destruction, but it can also affect organs [Morović-Vergles 2009]. In addition to RA, a number of differential diagnoses of OA of the knee should be considered [Clifton 2013]:

- Septic arthritis
- Pes anserinus tendinitis/bursitis
- Polymyalgia rheumatica

2.1.2 Etiology

OA can be classified as primary or secondary. It is classified as primary if the cause is not clearly identified, e.g. when ostensibly related to factors such as heredity, ethnic origin, age, sex, post-menopausal changes, overweight, lifestyle factors like alcohol and tobacco [Hackenbroch 2002; Michael 2010]. Secondary OA is defined as being the consequence of diseases, hereditary or acquired, or having other causes, like [Michael 2010]:

- joint malposition, such as varus-valgus knee stability
- congenital/malformation such as congenital dislocation of the hip
- metabolic disease, such as rickets, hemochromatosis, chondrocalcinosis or ochronosis
- endocrine disease, such as acromegaly, hyperparathyroidism or hyperuricemia aseptic osteonecrosis
- postoperative
- post-traumatic

Studies suggest that OA not only involves articular cartilage and subchondral bone, but also comprises the degradation of the ligaments, the capsule and the synovial membrane. These structures undergo uncontrolled catabolic and anabolic remodeling processes to adapt to local biochemical and biological signals [Clifton 2013, Sharma AR 2013].

Ling et al. describe the pathophysiological process of OA in which the matrix-degrading enzymes of OA cartilage are overexpressed, resulting in loss of collagen and proteoglycans from the matrix. As the disease progresses, reparative attempts are thwarted by cartilage degradation. Fibrillation, erosion and cracking initially appear in the superficial layer of cartilage and progress over time to deeper layers [Shari 2012]. Contrary to present classifications, a current study has found that immune activation and inflammation play an important role in OA and are major factors of ongoing joint degeneration [Liu-Bryan 2015].

2.1.3 Prevalence and Incidence of Osteoarthritis and Knee Osteoarthritis

Prevalence rates for OA observed in population studies in the US are comparable to those in Europe [Litwic 2013]. Surveys have shown that OA of the knee is the first or second most prevalent form of joint arthritis [Litwic 2013]. The age-standardized prevalence of radiographic OA of the knee in adults aged ≥ 45 years was between 19.2 % and about 43.7 % of participants aged over 80 years, hence prevalence increases with age [Litwic 2013].

Surveys represent the age- and sex-standardized incidence rates of symptomatic OA of the knee to be 240 per 100,000 persons a year. It increases rapidly around age 50 and levels off after age 70 [Oliveria 1995]. According to Murphy et al., the lifetime risk of developing symptomatic OA of the knee is estimated to be about 40 % in men and 47 % in women. Such a risk rises to 60 % in subjects with a body mass index (BMI) of 30 or higher [Murphy 2008].

2.1.4 Clinical Presentation

OA of the knee is primarily a clinical diagnosis which is based on history, physical examination and imaging procedures [Sinusas 2012]. The leading symptom of OA is joint pain, mostly becoming worse when the affected knee is in motion and improving when it is at rest [Sinusas 2012]. OA patients often describe the pain as a dull ache and also report joint locking or joint instability which results in loss of function [Di Cesare 2009].

According the survey of Zhang et al., three symptoms (i.e., persistent knee pain, minimal morning stiffness and reduced function) and three signs (i.e., crepitus, restricted movement and bony enlargement) appeared to be the most useful factors for the diagnostic evaluation of OA of the knee [Zhang 2009]. Furthermore, elevated sensitivity to cold and/or damp and joint-line tenderness are possible symptoms of OA of the knee [Arya 2013]. Permanent pain at rest, and/or at night can indicate advanced OA of the knee [Michael 2010].

2.1.5 Diagnostic Evaluation

Important components of the physical examination are inspection, palpation, testing of the range of movement and special functional tests like ligament stability, meniscus tests and gait analysis [Michael 2010].

X-ray examinations are used for primary diagnosis and to evaluate the progression of OA of the knee [Michael 2010]. Radiological signs of OA of the knee do not necessarily correlate with the clinical presentation. Only about 50 % of patients with radiological signs of OA report joint pain [Zhang 2009]. Similarly, only about 50 % of patients with chronic knee pain had radiographic evidence of OA of the knee [Miller 2001].

The typical radiological signs of OA of the knee can be seen on x-ray and are integrated into the staging system of Kellgren and Lawrence used for gradating OA [Kellgren 1957]:

Stage	Description
0	no abnormality, no radiographic features of OA
1	incipient OA, beginning of osteophyte formation on eminences
2	moderate joint space narrowing, moderate subchondral sclerosis
3	>50 % joint space narrowing, rounded femoral condyle, extensive subchondral sclerosis, extensive osteophyte formation
4	joint destruction, obliterated joint space, subchondral cysts in the tibial head and femoral condyle, subluxated position

There are additional diagnostic imaging options like ultrasonography and magnetic resonance imaging (MRI). Ultrasonography provides relevant additional diagnostic information on tissue-specific morphological changes not depicted by conventional radiography. However, it is dependent on the experience of the examiner [Podlipská 2016; Michael 2010]. MRI is considered the most accurate imaging modality in the assessment of OA of the knee [Roemer 2014]. Despite its high sensitivity, MRI is not usually used as an initial imaging technique for OA of the knee for practical and cost reasons [Podlipská 2016].

2.1.6 Conventional Treatment of Knee Osteoarthritis

The European League Against Rheumatism (EULAR), Association of the Scientific Medical Societies in Germany (AWMF) and other guidelines of expert organizations recommend an individual treatment depending on the severity of OA of the knee (pain, degree of OA, presence or absence of joint effusion) degree of activity, vocational situation, concomitant diseases, location and risk factors [Michael 2010; Jordan 2003; NICE 2008; Zhang 2008; Heidari 2011].

An optimal conventional OA therapy demands a combination of pharmacological and non-pharmacological modalities [McAlindon 2014; Hochberg 2012]. According to Michael et al. all therapy programs begin with consultation and patient coaching. Deterioration of the knee can be retarded, and in some cases the development of OA of the knee can be prevented altogether, by eradicating factors early which cause damage to the knee [Michael 2010]. Furthermore Michael et al. propose that patients should be advised regarding lifestyle improvements. On the one hand they describe how patients can perform sport in a way which is gentler for their knees, e.g. practicing cross-country instead of downhill skiing or the choice of adequate footwear. On the other hand, they address weight loss in obese or overweight patients. [Michael 2010]. Several studies confirm that obesity is a risk factor for OA of the knee [Muthuri 2011; Felson 1988]. According to the Framingham study, overweight individuals in their thirties who did not have OA of the knee were at greater risk of later developing the disease [Felson 1988]. Another study indicated that obese women had nearly 4 times the risk of OA of the knee as compared with non-obese women; for obese men, the risk was nearly 5 times greater [Anderson 1988].

As for the treatment of patients with OA of the knee, exercise has proved to be effective as a means of pain management and also of improving physical functioning e.g. muscle strengthening in the short term [Fransen 2009]. Furthermore, Michael et al. list physio-therapeutic measures for OA of the knee such as exercise therapy and physical measures consisting of ultrasound therapy, "electrotherapy, muscle stimulation, application of heat and cold, transverse friction, acupuncture and traction." Orthopedic aids can also be helpful, e. g. in alleviating stress on joints. [Michael 2010]

Knee orthoses are also intended to relieve pain and improve joint function [Kirkley 1999; Duivenvoorden 2015]. The aim of pharmacological treatment is to reduce pain and improve the physical functioning [Heidari 2011]. The standard practice in pain therapy is applied in accordance with the guidelines of the World Health Organization (WHO step-by-step plan). It subdivides pharmacological treatment into mild, moderate and severe analgesics [WHO 2008].

Paracetamol (Acetaminophen) is the analgesic of first choice for long-term use [Zhang 2008]. If there isn’t any significant or positive response to the use of paracetamol, then non-steroidal anti-inflammatory drugs (NSAIDs) are recommended (in oral or topical

form) [Michael 2010]. However, Michael et al. point out the risks related to the use of NSAIDs, in particular irritation of the gastrointestinal tract and adverse effects on renal function [Michael 2010]. Michael et al. describe a further possible treatment in the form of intra-articular glucocorticoid injections when signs of inflammation appear. This treatment, too, can have considerable side-effects such as complications for diabetic patients with hyperglycemia or septic arthritis [Michael 2010].

According to Michal et al., surgery is to be chosen as a final resort only after attempts of conservative treatments have failed [Michael 2010].

Arthroscopic surgery in patients with advanced OA of the knee has been discussed controversially in recent years. There is a variety of co-pathologies that can be effectively addressed with arthroscopic surgery [Niemeyer 2012]. Moseley et al. confirmed in a controlled trial involving patients with OA of the knee that the outcomes after arthroscopic lavage were no better than those after a placebo procedure [Moseley 2002].

2.2 Ayurveda

Ayurveda is a Sanskrit compound of two words, ayus meaning "life" and veda meaning "knowledge" or "science", or more precisely "science of the lifespan" [Kessler 2013]. First mentioning of medical content in Indian texts can be dated back approximately to 1200 BC in the Atharvaveda [Yukti 1997].

Ayurveda is recognized as a Traditional Medicine [WHO 2000] by the World Health Organization (WHO) which developed guidelines for education, research, pharmacovigilance and medical practice [Kessler 2012; CCRAS 2015; WHO 2001, 2004, 2013; AAPI 2015]. In India, Ayurveda is widely used and is regulated by its own ministry (AYUSH) and legally put on equal footing with conventional medicine [CCRAS 2015]. There are more than 450,000 Ayurvedic physicians registered in India alone, educated in over 250 universities and colleges recognized by the Indian Government [AAPI 2015]. Ayurveda plays an increasingly important role in the US and European countries, and at present it belongs to the fastest-growing complementary therapies in Europe [Grayson 2011; Kessler 2007]. There, professional associations are trying to set standards for Ayurveda practice and education in order to assure quality, but national licensures for Ayurveda are still pending [NAMA 2016; AAPNA 2007; Baghel 2015].

Different philosophical streams in ancient India influenced Ayurvedic medicine, above all the Samkhya-Philosophy, in which human beings (the microcosm) are believed to correspond to the universe (the macrocosm). As an integral part of nature, human beings are governed by natural laws. Ayurveda describes and recommends a suitable lifestyle which is based on these principles to achieve and maintain homeostasis. An important principle of Ayurveda is empowering patients, recognizing that individuals can care for themselves by striving for balance necessary for good health. The loss of balance can be caused by unhealthy dietary habits, physical inactivity, unhealthy behavior patterns, incorrect use of the body, sensory organs and mind [Kessler 2007].

Ayurveda understands human life as an interaction of three vital functional principles or doshas (vata, pitta, kapha), seven body tissues or dhatus (rasa, rakta, mamsa, meda, asthi, majja, shukra/artava) and the metabolic waste (feces, urine, sweat). The cause of most illnesses in Ayurvedic medicine lies either in disturbances in the doshas or in a deficiency in dhatus and agnis (the digestive and thermic principle of the body) [Ranade 2004].

The "Panchamahabhuta-Theory"

The theory of the five elements "Panchamahabhuta" provides the basis for all further concepts of Ayurveda. According to Ayurvedic thought, the five basic elements which are the basis for all matter in the universe are akasha (space), vayu (air), agni (fire), jala (water) und prtivi (earth). They manifest themselves in the human body as energy forms or vital functional principles called doshas [Murthy 2017].

Doshas

The doshas define not only the physical constitution, but also the physiology, patho-physiology, symptomatology and therapy of Ayurveda. Furthermore, different influences like effects of behavior patterns, stages of life, daytimes and seasons or climate can be categorized with the doshas. They manifest themselves in three functional principles vata, pitta and kapha. [Murthy 2017]

- Vata is a composition of the elements space and air. It is the most mobile functional principle of the organism and regulates physical systems such as respiration, excretion or the musculoskeletal system. Vata plays a decisive role in e.g. enthusiasm or creativity [Murthy 2017].
- Pitta is a composition of the elements fire and water. It is responsible for the functional principle of metabolism. It plays an important role in processes such as digestion and balance of heat. On a mental level, pitta is most of all associated with Intelligence and rational thinking [Murthy 2017].
- Kapha is a composition of the elements of water and earth. It is the structuring functional principle of the organism. It is responsible for physical shape, maintenance of cell adhesion and networking. On a mental level, kapha is predominantly associated with stability and memory [Murthy 2017].

The concept of the seven body tissues or dhatus plays a key position in the Ayurvedic physiology and anatomy. The seven dhatus are involved in the building and functionality of the organs and body tissues [Ranade 2004].

Dhatus - The body tissues and their equivalent in conventional medicine

Rasa	- plasma
Rakta	- blood
Mamsa	- muscle tissue
Meda	- fat tissue
Ashti	- bone tissue
Majja	- bone marrow tissue, nerve tissue
Sukra, Artava	- reproductive tissue

Agni

The agni-principle controls the balance between food intake, its transformation and waste elimination, which is yet another factor for maintaining health [Sharma RK 2002; Kessler 2015]. Agni, which literally means "fire", describes the digestive and thermic principle which ensures the transformation of nutrition throughout the body. It functions at both the physical and mental levels in various bodily processes related to digestion, metabolism and assimilation [Ranade 2004].

Prakriti

Prakriti describes the individual constitution of human beings. It is determined at the time of conception through an ideal balance of the three doshas vata, pitta and kapha of an individual. Furthermore, it is influenced by external factors like nutrition, social environment, climate, emotions and individual behavior [Ranade 2004].

2.2.1 Ayurveda and Treatment of Osteoarthritis

The following section is based on the paper of Kessler et al. [Kessler 2018]. According to Sharma and Upadhyaya, Ayurveda is especially effective in treating chronic diseases of the musculoskeletal system, to which OA can be counted [Sharma RK 2002; Upadhyaya 1993]. The concept of Ayurveda is integrated and multidimensional. Consequently, the Ayurvedic treatment of OA patients follows complex diagnostic and therapeutic pathways [Kessler 2018].

In an Ayurvedic context, an essential factor for therapeutic success is a multimodal and individually adjusted therapy making use of manual therapies, lifestyle advice, nutrition therapy, dietary supplements, yoga, meditation and spiritual practices [Gupta 2009].

The nomenclature of Ayurveda does not include an exact equivalent of the conventional medicine disease entity OA [Kessler 2018]. In traditional Indian medicine, OA belongs to the cluster of vata-diseases in which the kinetic vata-principle plays the most important role. Thus, a reduction of the aggravated vata-principle is the main factor of a complex Ayurvedic OA treatment-approach [Kessler 2015]. In Ayurvedic texts, there are four different nomenclatures for disease entities which approximately correspond to OA: sandhivata, sandhigatavata, khudavata, and jirnavata [Murthy 2017]. The Ayurvedic fraternity generally uses the term sandhivata for OA, where sandhi means "joint" and vata is an expression for the "kinematic principle" [Kessler 2018]. In Ayurveda the effects of sandhivata are caused by poor nutritional and lifestyle habits, as well by an ongoing aging process. These effects lead to a decrease of ‘body elements’ (dhatukshaya) and an aggravation of vata, which is responsible for all movements, musculoskeletal and neurological functions in the body [Kessler 2018]. The aggravated vata causes ruksyata (dryness), laghutva (lightness or porousness) or kharatva (coarseness) in the joints [Kessler 2018]. The typical symptoms of the disease itself appear when the aggravated vata affects any of the joints and weakens the structure and function of the joint [Kessler 2018]. The effects described in both sandhigatavata and OA are similar. The main feature in sandhivata is sandhisula, i. e. pain in the affected joint [Kessler 2018]. Other characteristic features are sotha (swelling), stabdata (stiffness), atopa (crepitus) and difficulties in performing the functions of the joint involved [Sharma RK 2002; Bhavaprakasha 1998; Srikantha Murthy 1999; Voga Ratnakara 2005].

Rastogi et al. point out that Ayurveda is a whole medical system. They represent the evaluation of Ayurveda results within the methodological framework of conventional clinical research in which interventions are fragmented [Rastogi 2013]. Moreover, a systematic review of 33 recent studies came to the conclusion that most trials (91 %) focused on herbal Ayurvedic preparations as a single intervention [Kessler 2015].

In 2013, according to Witt et al., there was a particular need to evaluate Ayurveda as a whole medical system using conventional medicine as well as traditional Ayurvedic diagnostic aspects. No clinical study on OA had been performed which took a multi-dimensional approach of Ayurveda as a complex and whole medical system into account. [Witt 2013]

According to Gupta et al., complex treatments of a whole medical system such as Ayurveda follow the premise that the combination of different treatment elements yields synergistic effects, thereby affecting the outcome [Gupta 2009]. However scientific data was missing to support a clinically relevant effect of such a complex treatment approach and to compare its effectiveness with that of conventional medical standard care for OA. Furthermore, the reliability of diagnostic Ayurvedic tools has been strongly questioned in the past [Witt 2013].

This research project aimed to attain first findings on complex Ayurvedic treatment approaches in general and specifically in the case of OA of the knee within a European context [Kessler 2018]. Witt et al. pointed out that study results could provide significant data on the effectiveness and safety of complex Ayurvedic therapies and enhance the global acceptance of Ayurveda within the framework of a whole medical system. In addition, Witt et al. contended that such a study could be an important step toward implementing Ayurveda as an OA treatment within the context of evidence-based medicine [Witt 2013]. The main goal of this project was to conduct a comparative effectiveness clinical trial comparing complex Ayurvedic care to conventional conservative care in the treatment of knee osteoarthritis patients over a 12-week period in a German setting with changes on the WOMAC Index as the main outcome.

2.2.2 Integrative and Complementary Medicine OA Management

In this study the effectiveness of Ayurvedic therapy in OA of the knee has been investigated, comparing it to conservative conventional therapy. Similar studies with an emphasis on Traditional Indian Medicine do not exist to date. However, this chapter gives an overview of a selection of publications of the last decades, focusing on Integrative and Complementary Medicine for the treatment of knee OA.

In the year 2004, Vas et al. [Vas 2004] published a paper that presents acupuncture as a complementary therapy to the pharmacological treatment of OA of the knee in a randomized controlled trial. Another study, presented by Karner et al., investigated the effects of acupuncture in a double-blinded randomized trial in OA of the knee [Karner 2013]. A different approach was investigated by Lauche et al.: the authors published a paper that presents a systematic review and meta-analysis of the effectiveness of medical leech therapy for knee OA [Lauche 2014]. An additional publication of Lauche et al. aimed to test the effects of cabbage leaf wraps (CLWs) in the treatment of knee OA [Lauche 2016] as a complementary approach to medication intake. Another approach was presented by Wang et al. [Wang C 2016]. The authors of the study compared the effectiveness of Tai Chi with physical therapy for OA of the knee. Bannuru et al. performed a meta-analysis in 2018 with a focus on the efficacy of Curcumin and Boswellia for knee OA [Bannuru 2018]. In another study by Wang et al. from 2018 yoga was investigated as a treatment method for knee OA and rheumatoid arthritis in a meta-analysis [Wang Y 2018]. Perlman et al. presented a study in 2019 in which patients with knee OA were treated either with a whole-body Swedish massage or with light-touch or the so-called “usual care” [Perlman 2019]. In 2020 Wang et al. [Wang Z 2020] used an herbal remedy, Curcuma longa, for the therapy of patients with knee OA. The study focused on the effects on localized effusion or synovitis in patients’ knees. Singhal et al. took a similar path examining the effects of turmeric, a constituent of the Curcuma longa root, in comparison to paracetamol for pain relief in patients with knee OA [Singhal 2021].

Further discussion of the results of these studies in comparison to the study described here takes place in **chapter 5.5**.

3. Methods

The following chapter is based on the study protocol of Witt et al. [Witt 2013] and the description of methods presented in [Kessler 2018]. The figures and tables herein reproduced are published in [Kessler 2018].

3.1 Study Design

The aim of the present study was to compare the effectiveness of a complex individualized Ayurvedic treatment based on Ayurvedic diagnosis with conventional guideline care in patients with OA of the knee. The study was performed as a prospective, multi-center, randomized, controlled clinical trial with two treatment arms:

1. Ayurveda treatment,
2. Conventional treatment.

In this context, “multi-center” describes that the study was carried out in two different centers in Berlin, where the treatment-interventions took place in outpatient settings:

1. Immanuel Hospital Berlin-Wannsee, (Department of Complementary and Integrative Medicine. Department of Orthopedics: lower extremities, endoprothetics, foot and spine surgery; in cooperation with the Department of Physiotherapy).
2. Health care center “Sonne und Mond”, Berlin-Prenzlauer Berg. Practice for Orthopedics and Surgery Dr. Bauwens and Dr. Bröcker; in cooperation with the Practice for Physiotherapy and Sports Therapy Marion Prüßing, Berlin-Mitte).

3.1.1 Randomization

An equal block-randomization with variable block lengths, stratified for study site, was used. Patients were randomized to Ayurvedic or conventional treatment in a 1:1 ratio [Witt 2013]. An independent statistician used SAS (Serious Adverse Events) (version 9.1, SAS Inc, Cary, NC) to generalize a randomization list. The data manager transferred the randomization list into a secure database (Microsoft Office Access 2007), where the randomization list was not accessible to any other staff members. Each patient could be registered and randomized only once, and the database did not allow

deleting any patient data. The allocation of participants to the two treatment arms was performed with sealed randomization-envelopes [Witt 2013]. Trial statisticians, data entry personnel as well as the funding source were all blinded to treatment assignment throughout the study. [Kessler 2018]

3.1.2 Ethics

The trial was registered at clinicaltrials.gov under NCT01225133 and was approved by the Charité University ethics committee (EA1/124/10). This study followed the Declaration of Helsinki and Good Clinical Practice guidelines for trial conduct. All study participants provided written informed consent and were not compensated for participation in the study. [Kessler 2018]

Due to changes in ethical regulations during the trial, one amendment was made regarding the provision of nutritional supplements. Thereafter, the remaining 24 study participants from the Ayurveda group were no longer given nutritional supplements but were advised to increase the food intake of the previously supplemented nutrients wherever possible. [Kessler 2018]

3.2 Participants

Among the participants, 70 % were recruited via newspaper advertisements. The remaining 30 % were recruited by physicians from the trial center clinics or contacted the centers themselves, because they had heard about the trial. Participants were scheduled to an enrollment visit only after successfully undergoing pre-screening over the phone. [Kessler 2018]

Inclusion and exclusion criteria for all participants followed conventional medicine diagnosis, whereas the individualized treatment in the Ayurveda group was chosen according to Ayurveda diagnosis. The traditional Ayurveda diagnosis was performed for all participants who fulfilled the eligibility criteria. The treatment protocol for each patient followed the Ayurveda diagnosis in the Ayurveda group and conventional medicine diagnosis in the control group. [Witt 2013]

3.2.1 Inclusion Criteria

As described in [Witt 2013], inclusion criteria were defined as:

- male and female patients,
- age 40-70 years,
- pre-diagnosed, confirmed and documented diagnosis of OA of the knee. Diagnosis performed by a medical specialist (orthopedic surgeon, surgeon, radiologist) according to the American College of Rheumatology criteria study [Hochberg 2012],
- documented radiologic changes of the knee-joint Kellgren and Lawrence criteria [Kellgren 1957] ≥ grade 2 in conventional X-ray or MRI-scan,
- mean average pain intensity of 40 mm or more on a 100 mm visual analogue scale in the 7 days before baseline assessment,
- written informed consent

3.2.2 Exclusion Criteria

As described in [Witt 2013], exclusion criteria were defined as:

- Pain in the knee caused by
    - congenital dysplasia of the affected knee,
    - rheumatoid arthritis,
    - autoimmune diseases,
    - malignancies,
    - knee surgery,
    - arthroscopy;
- administration of chondroprotective drugs in the preceding 12 weeks to enrollment;
- intra-articular injection into the affected knee-joint during the preceding 12 weeks to enrollment;
- beginning of a systemic medication with corticosteroids within the preceding 12 weeks to enrollment;
- beginning of any new treatment for OA during the 4 weeks preceding enrollment (with the exception of analgesic treatment with paracetamol or NSAIDs);
- pregnancy or breastfeeding;

- acute mental disorders;
- serious acute organic diseases;
- serious chronic co-morbidity;
- obesity WHO-grade II/III;
- blood coagulation disorders;
- coagulation-inhibiting medication other than aspirin and clopidogrel;
- invasive measures performed at the affected joint during the preceding 12 weeks or planned within the following 12 months;
- in the process of applying for pension or disability benefits;
- simultaneous participation in any other clinical trial;
- participation in a clinical trial during the 6 months before inclusion into this trial; and
- missing written informed consent form.

3.3 Outcome Parameters and Measuring Devices

Primary and secondary outcome were assessed using patient questionnaires which are validated and reliable measuring instruments. Primary outcome was the change on the Western Ontario and McMaster University Osteoarthritis (WOMAC) Index after 12 weeks. [Kessler 2018]

Furthermore, the following secondary outcomes were collected [Kessler 2018]:

- WOMAC subscales (pain, function and stiffness) [WOMAC 2015],
- Pain Disability Index (PDI) [Dillmann 1994],
- Pain Experience Scale (SES) [Geissner 1996],
- Numeric Rating Scales (NRS, range 0-10) for pain and sleep quality [Huskisson 1993; Westhoff 1993],
- health-related quality of life by using Short Form-36 (Health Survey, SF-36) [Bullinger 1998],
- Profile of Mood States (POMS) [Grulke 2006],
- 7-point Likert Scales for general health-related patient satisfaction [Likert 1932],
- a patient diary for rescue medication use,
- safety (Adverse Event (AE) and Serious Adverse Event (SAE).

3.3.1 WOMAC Index

The WOMAC (Western Ontario and McMaster Universities Osteoarthritis) Index was measured for all patients and the mean of these values was taken. The measurements were collected over a period of 12 weeks. [Kessler 2018]

The WOMAC Index is the most widely utilized self-report measure for OA and reflects the clinical severity of the OA of the knee with the help of subjective and objective criteria of the patient [Kellgren 1957; McConnell 2001].

It consists of 24 items divided into 3 subscales:

- Pain questions (5 items) cover everyday activities such as walking, using stairs, lying in bed, sitting and standing.
- Stiffness questions (2 items) cover stiffness after first waking and later in the day.
- Physical Functioning questions (17 items) cover everyday activities such as stair use, rising from sitting, standing up from a sitting or lying position, bending, walking, getting in and out of a car, shopping, putting on or taking off socks, rising from bed, lying in bed, getting in or out of bath, sitting, getting on or off toilet, doing heavy and light household duties.

Internationally, many different validated versions exist for several countries and languages. In this study, the validated German version of the WOMAC was used with a score range varying from 0 to 240 [Stucki 1996]. The score ranges of the three subscales are as follows:

- Pain (range 0-50),
- Stiffness (range 0-20) and
- Function (range 0-170).

Higher scores correspond to worse pain, stiffness, and functional impediment.

3.3.2 Pain Disability Index (PDI)

The Pain Disability Index (PDI) is a quick instrument for measuring the degree of pain a patient is experiencing. The index was introduced by St. Louis University Medical Center in the 1970s [Chibnall 1994; Pollard 1984; Tait 1990]. The PDI is a self-reporting test for the participants used to evaluate and to monitor the effectiveness of interventions over time. In the present study, the German version was used, which rates how much pain interferes in seven areas of personal life, i.e. familiar and domestic responsibilities, recreation, social activities, occupation, sexual life, ability of self-care and vital activities (like eating, sleeping, breathing) [Dillmann 1984]. Participants use a 0 (no disability) to 10 (total disability) numeric rating scale.

3.3.3 7-Point Likert Scale

A Likert Scale is a descriptive scale used to analyze personal attitudes. It is a bipolar scale running from one extreme through a neutral point to the opposite extreme. Participants express their level of agreement with each of several statements (in the present study seven statements), with a number of given response options varying from "strongly disagree" to "strongly agree". The point score of the individual answers are summed up. [Titchener 1921; Likert 1932]

3.3.4 Pain Experience Scale (SES)

The Pain Experience Scale (SES from the German Schmerzempfindungs-Skala) enables the measurement and differentiated description of subjectively perceived pain. The patient questionnaires consist of 24 items covering both affective and sensory pain perception. The latter is composed of three subdimensions (pain description according to rhythm, local penetration and temperature). [Geissner 1996]

3.3.5 Numeric Rating Scale for Pain

The Numeric Rating Scale (NRS) for Pain is a one-dimensional Scale for measuring intensity and quality of pain, using an equidistant numeric rating scale ranging from 0 to 10 (NRS with 0 = no pain and 10 = worst pain imaginable). The endpoints represent the extremes of the pain experience. Participants are asked to circle the number on a horizontal line that represents the pain level [Dijkers 2010; Huskisson 1993; Westhoff 1993].

3.3.6 Short Form-36 Health Survey (SF-36)

The SF-36 is considered to be the best-investigated instrument for measuring health-related quality of life [Garratt 2002]. The German validated translation was used. The questionnaire contains 36 questions with Likert scales which cover 2 to 6 levels. Eight health dimensions are addressed in subscales ranging from 1 to 4 for physical and 5 to 8 for psychological health aspects. In the present study, only the sum scores are presented. High scale values in the SF-36 correspond to a better state of health [Bullinger 1995].

3.3.7 Profile of Mood States (POMS)

The questionnaire "Profile of Mood States" (POMS) ranks among the most often used instruments for measuring mood state [Grulke 2006]. It represents a psychological rating test used to assess distinct mood states. The original American version measures six different dimensions of mood swings with 65 items in total over a defined period of time (max. 1 week) [McNair 1981]. A five-point scale ranging from "not at all" to "extremely" is administered by experimenters to patients to assess their mood states. In the German-speaking area, the abridged version as prepared by Biehl, Dangel, Reiser and Bullinger has taken root [Grulke 2006; Bullinger 1990]. The German version has been applied in the present study. It consists of 35 items, divided into 4 dimensions: depression factor (14 items), fatigue factor (7 items), vigor factor (7 items) and anger factor (7 items). Advantages of using this assessment include the simplicity of administration and ease of participant understanding.

3.3.8 Patients' Diary

All participants were asked to maintain a diary on a daily basis describing the frequency of medication taken on demand. Furthermore, the Ayurveda group was asked to document the fulfillment of their yoga exercise requirements. [Witt 2013]

3.3.9 Assessment of Safety

Definitions

Adverse effects were all unwanted or undesirable subjective or objective symptoms, disorders, illnesses, diseases or accidents which occurred during the study period and were deemed by the patients or physicians to be causally related, or possibly causally related, to the study interventions. [Witt 2013]

Adverse events (AE) were all unwanted or undesirable subjective or objective symptoms, disorders, illnesses, diseases or accidents occurring during the study period, regardless of whether they were causally linked to the study intervention or not [Witt 2013]. In addition, Serious Adverse Events (SAE) were defined as adverse events occurring during the study period which were life-threatening or presenting a serious harm to health, in particular those

- associated with relevant or permanent disability,
- necessitating in-patient treatment,
- involving malignant diseases,
- medically relevant and leading to a medical intervention to avoid one of the above-mentioned problems [Witt 2013].

Documentation

As described in [Witt 2013], in this study, adverse effects and serious adverse events were documented. During each visit, the trial physician inquired whether the patients had experienced any adverse effects or serious adverse events. These were recorded in the following way:

- Mild adverse effects were listed in the normal treatment or study visit documentation.
- Moderate adverse effects were documented in a special form with details on type, beginning and end of the adverse effect, intensity, course, causal relationship to the therapy, potential interventions, clinical course and outcome.
- Serious adverse effects or events were followed up until a final outcome was clear, even if this extended beyond the study period. All effects and events were documented in the same form and in the same way as moderate adverse

effects. In addition, these events were reported per telephone or fax (documentation form) within 24 hours to the coordinating center. The intensity of adverse events and effects were classified in the following manner:

(1) mild: no interference with normal activities,

(2) moderate: impairment of normal activities,

(3) serious: normal activities impossible.

The causal relationship with the study interventions was assessed according to the following scale:

(0) none: the effect or event was definitely due to other causes,

(1) possible: a causal relationship could not be ruled out,

(2) likely: a causal relation was highly plausible,

(3) certain: other causes could be ruled out,

(4) unclear. [Witt 2013]

3.4 Duration and Visits

All outcome data were obtained at specific points in time: at baseline, after 6 and 12 weeks, and after 6 and 12 months. Questionnaires and diaries were handed out at baseline, before randomization. In week 6 and week 12, study nurses requested all patients to complete questionnaires and return them in sealed envelopes. As the treatment time during the study ended after 12 weeks, patients were asked to send in questionnaires as well as the diaries to the study office after 6 and 12 months. Adverse events (AEs) were evaluated by trial personnel in a standardized way at each visit. They were also documented by patients at the end of week 6 and week 12. [Kessler 2018]

Figure 3.1 shows the design of the study.

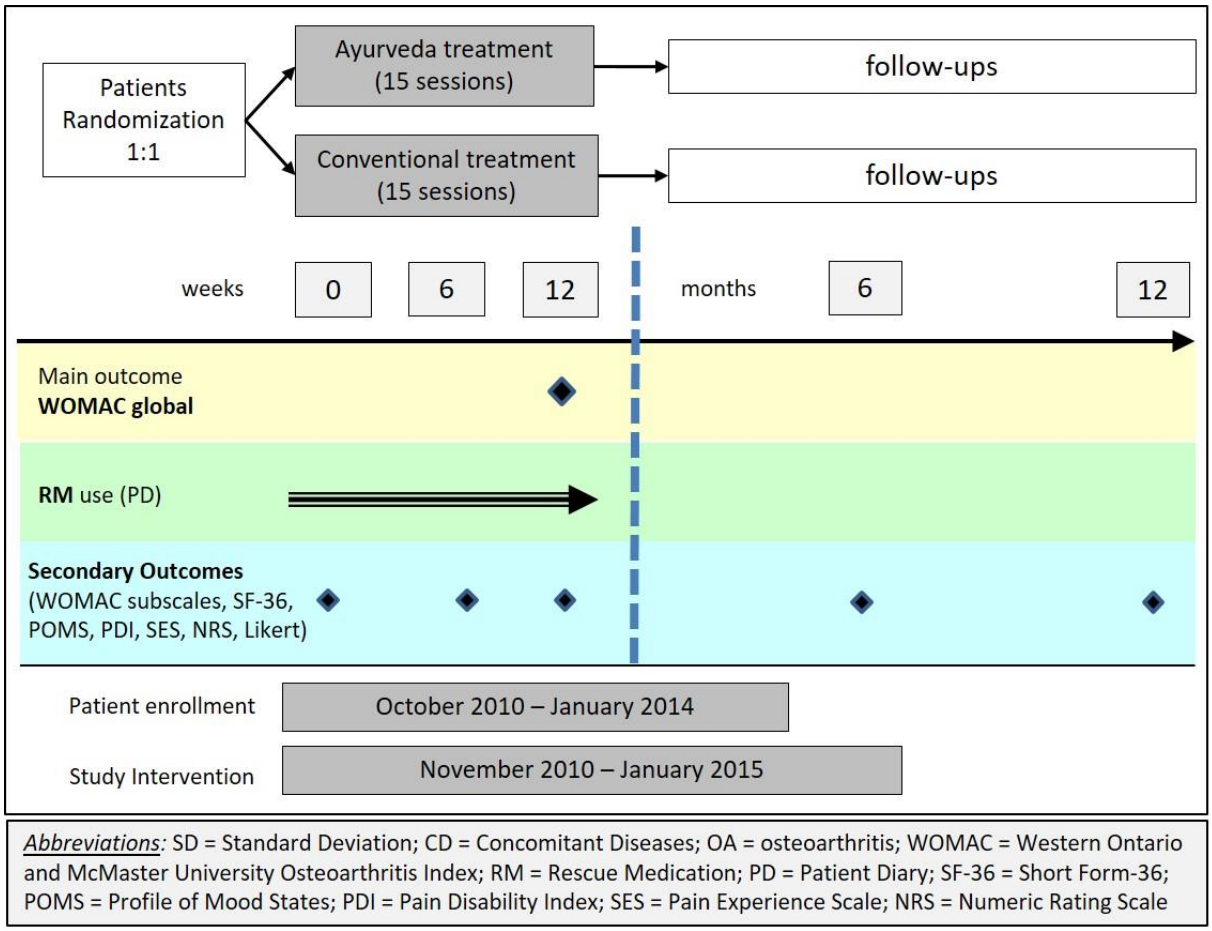

Figure 3.1: Study Design [Kessler 2018]. (Reprinted with permission of the authors from open access publication.)

So-called case report forms (CRF) were used to record data. All processes and data handling were defined according to standard operating procedures (SOP) of the Institute of Social Medicine, Epidemiology and Health Economics of the Charité University Medical Center. [Kessler 2018]

3.5 Statistics

3.5.1 Hypothesis for Effectiveness

As described in [Witt 2013], this study was designed to test whether or not the mean effectiveness (as measured by the primary outcome parameter) of the Ayurvedic treatment is superior or inferior to the mean effectiveness of the control group:

- Null hypothesis (H_0) was defined as:
  "There is no difference between the Ayurvedic treatment and the conventional treatment regarding their effects."
- The alternative hypothesis (H_A) was formulated accordingly:
  "The difference between the WOMAC Index mean pain scores of the Ayurvedic treated group and the conventional treated group is positive after 12 weeks of treatment."

This study was designed to have 80 % power to detect a 10-point improvement (change to baseline) on the WOMAC Index between both observed groups after 12 weeks of treatment (pooled standard deviation=20, two-sided t-test α=0.05). To achieve statistical certainty, at least 64 participants per group were needed. To account for potential dropouts, it was planned to include 74 participants per group. The primary analysis population was the intention-to-treat (ITT) population including all randomized participants who provided baseline data for the primary outcome. [Witt 2013]

3.5.2 Statistical Approach

One of the main entities in statistical analysis is the confidence interval, which provides information about a range in which the true value lies with a certain degree of probability [Cox 1974; Kendall 1973]. According to Du Prel et al. the confidence interval offers details regarding "the direction and strength of a demonstrated effect" [Du Prel 2009]. In addition to this in many "exploratory studies" statistical key figures like p-values are used. Du Prel describes p-values as an indicator to allow the identification of any "statistically noteworthy findings". P-values in scientific studies are used to determine whether a null hypothesis devised before carrying out the study is to be "accepted or rejected". Both statistical measures enable conclusions to be drawn about the statistical plausibility and

clinical relevance of the study findings. However, it is useful to provide "both measures in statistical" explorations since they "provide complementary information". [Du Prel 2009]

As a first step of a confirmatory study, a null hypothesis (H_0) has to be defined which has either to be rejected or confirmed by the means of statistical analysis. Therefore, in order to show that Ayurveda and conventional treatments are not equivalent, a null hypothesis (H_0) has been formulated in accordance to Du Prel's approach [Du Prel 2009]: There is no difference between the Ayurvedic treatment and the conventional treatment regarding their effects. Hence, the alternative hypothesis (H_A) has to reveal that there is a difference in the effects as a result of different treatments. H_A has been formulated as a one-tailed hypothesis in the exclusive expectation of a positive effect: The difference between the WOMAC Index mean pain scores of the Ayurvedic-treated group and the conventionally treated group is positive after 12 weeks of treatment.

The p-value is a probability, which is the result of a statistical test. This probability reflects the measure of evidence against the null hypothesis. Low p-values correlate with strong evidence. The results are deemed "statistically significant" if the p-value is below a predefined limit. [Du Prel 2009]. P-values as single values are quite useful in order to decide whether a value is greater or less than a specified limit, a result thus "becoming" significant or not. However, the result might be misleading since it is a result of a statistical evaluation. [Du Prel 2009]

In order to underline a clear distinction between the effects of Ayurvedic treatment and conventional treatment in this study a p-value of $p \leq 0.001$ is being used, which suffices demands in many medical explorations. Values below ≤ 0.001 are being referred to as "statistically highly significant" results. [Du Prel 2009] In summary, the smaller the p-value, the more reliable is the alternative hypothesis (H_A). [Du Prel 2009]

Furthermore, in order to distinguish the null hypothesis H_0 and the alternative hypothesis H_A, a significance level α has to be defined in advance. In the present study a level of significance of $\alpha = 0.05$ has been chosen. [Du Prel 2009] The level of significance indicates how high is the probability is that the alternative hypothesis has to be rejected, even though the hypothesis is right. [Du Prel 2009]

3.5.3 Statistical Analysis

The following section is based on the paper of Kessler et al. [Kessler 2018]: The primary outcome of the study was the change of the WOMAC Index after 12 weeks. Using maximum-likelihood-based regression methods, missing data were multiply imputed. In total, 20 complete data sets were generated and combined adequately. A linear regression was performed on the data sets by using the Generalized Linear Mixed Model (GLMM), including the treatment group as a fixed factor. Results were summarized as adjusted WOMAC mean values per group with 95 % confidence intervals and the two-sided p-value for the treatment group comparison.

Data Analysis

The used approach for data analysis was described by Kessler et al. [Kessler 2018]. The authors state how ANCOVA (*Analysis of Covariance*) models were applied as "independent variables" for sensitivity analysis for WOMAC Index and WOMAC sub-scales after 12 weeks of treatment [Kessler 2018]. "Treatment group" and "gender" were defined as "fixed factors" for the data; "baseline values" and "participants´ expectations" were defined as "linear covariates". Cohen's d [Cohen 1988] and "its confidence intervals with d > 0.5" expressing "clinically relevant effect sizes" were applied to measure the extent of "effect sizes between and within groups for the primary endpoint" [Kessler 2018]. In order to quantify the amount of the "total variance in the "variable 'WOMAC Index after 12 weeks'" the "Partial η^2" was introduced. It represents an additional measure of the effect size. However, this proportion was associated with specific independent variable like "treatment group" or "expectations" [Kessler 2018]. Lastly, with the use of "univariate t-test" the differences between the means of the "within-group changes" for "primary and secondary outcomes" were calculated [Kessler 2018]. "Chi-Square tests" were applied to carry out "treatment responder analyses" [Kessler 2018]. A reduction of at least 12 points on the WOMAC Index was defined "as a treatment response for the main outcome parameter" [Kessler 2018]. All analyses of statistical data were performed blind and before the "randomization code" was broken [Kessler 2018]. Analyses were carried out with the use of SPSS (release 23.0, IBM, Armonk, NY, USA, 2015) [Kessler 2018].

3.6 Embedded Diagnostic Pilot Study

The following paragraph is based on a study from 2010 by Kessler et al. [Kessler 2019]. The authors describe how "a diagnostic reliability study" was implemented within the present study encompassing 30 participants and four Ayurveda specialists. The aim was to evaluate "inter-rater reliability (IRR)" "of Ayurvedic diagnosis" for knee OA patients. In this embedded study, a semi-structured form for registering the medical history of patients was used to diagnose participants "in a sequential order by all" specialists. As a part of the consensus process, a nominal group technique, i.e. problem identification, solution generation, and decision making, was carried out to agree on the aspects "to be diagnosed". With the help of Cohen's kappa and Fleiss' kappa for three or more raters an analysis of the IRR (*Inter-Rater Reliability*) was completed. In this way "a chance-corrected" gage of consensus between raters was ascertained.

Furthermore, Kessler et al. describe that in total "120 different ratings and 30 consensus ratings" were carried out [Kessler 2019]. On the one hand, a high measure of agreement was achieved for principal diagnostic factors and the ultimate "Ayurveda diagnosis". In particular, there was a broad agreement of 95 % on the principal diagnosis. But on the other hand, the related kappa values turned out fair to poor, with "k values between 0 and 0.4", on kappas for "inter-rater agreement" on main diagnostic factors like prakriti and agni. In particular, the accordance on "disease-related entities" was higher than "that on constitutional entities". [Kessler 2019]

However, Kessler et al. come to the conclusion that this study is "the first diagnostic study" which is included within a clinical investigation on knee OA patients using a "multimodality whole systems" concept [Kessler 2019]. The authors claim that the results revealed an apparent difference between the high correspondence on the agreement concerning the "final diagnosis" on the one hand and the poor convergence on specific "diagnostic details" on the other [Kessler 2019]. Furthermore, the authors find that the sample size of subsequent "diagnostic studies" should be larger, and the procedures used should be better adapted to the characteristics of "traditional whole systems of medicine" [Kessler 2019]. By implementing highly detailed, newly structured patient history forms, equal attention should be put on all fundamental diagnostic factors of Ayurveda, whether they be "constitutional" or "disease specific" [Kessler 2019].

3.7 Interventions

3.7.1 Ayurveda-Intervention

The following sections are based on Kessler et al. [Kessler 2018]. An international team of experienced Ayurveda and orthopedic experts from three different countries (India, Germany and Italy) designed the trial interventions. A Delphi method was utilized for the surveys [Upadhyaya 1993]. Classical Ayurvedic literature (Ayurveda group) [Sharma RK 2002] and current guidelines for patients of the conventional group were applied [DGOOC 2002; AAOS 2008].

The experts for Ayurvedic diagnosis and treatment were all physicians with both conventional and Ayurveda training. The selected physicians had different qualifications depending on their individual backgrounds. Those from India had completed a regular curriculum for Ayurveda at an Indian university "(B.A.M.S., Bachelor of Ayurveda Medicine and Surgery)"; those from Europe had acquired a minimum of 500 hours of academic instruction in Ayurveda and a minimum of two years of uninterrupted clinical practice with Ayurveda. [Kessler 2018]

Additional Ayurvedic therapists, with comprehensive expertise in "manual therapies, nutritional advice, lifestyle advice and yoga therapy", had all obtained a minimum of two years of uninterrupted clinical practice in their particular specialties. [Kessler 2018]

Medical specialists in the fields of orthopedics or orthopedic surgery determined the treatments for participants in the conventional group; these medical specialists were all "board-certified medical doctors". Additionally, the remaining conventional therapists, i.e. physiotherapists or occupational therapists, had at least two years of uninterrupted clinical experience after completing "licensed training" in their respective areas of expertise. [Kessler 2018]

Participants were treated in "two public hospital outpatient clinics and two hospital-affiliated private outpatient clinics for Ayurveda, orthopedics, orthopedic surgery, physiotherapy and occupational therapy in Berlin, Germany." A total of "5 specialized physicians (2 Ayurveda, 3 conventional MDs) and 20 specialized therapists (12 Ayurveda [8 for manual therapies, 2 for yoga, 2 for nutrition and lifestyle], 8 conventional [6 for

physiotherapy, 2 for nutrition and occupational therapy])" carried out the treatments. [Kessler 2018]

The multi-component Ayurveda intervention generally followed the treatment principles of Ayurveda. It was individualized and the customized treatment was as follows (**Figure 3.2**):

- Manual treatments / body massages (abhyanga) were provided using classical Ayurvedic massage positions and knee poultices/ specific local applications (lepas, janu-bastis, kati-bastis) focusing on the affected knee(s) and knee-associated structures.
- Physicians selected Ayurvedic oils and fats according to the constitution of the patient and to the individual progression of the disease**.** The most commonly used oil was mahanarayan, alternative oils were dhanvanataram, shulahara, kshirabala and murivenna). Exclusively Ayurvedic products which were available over the counter in Germany were used for the treatments.
- Svedana, in the form of local sudation treatments and generalized sudation measures, was provided during and/or following massage treatments, individualized with respect to time and intensity depending on the patient's progression of the disease. Furthermore, applications of wet and hot cloth on affected knees were given (pinda-sveda).
- The use of personalized nutritional counseling was made according to the principles of Ayurvedic dietetic treatment, including standardized diet-sheets. The focus was on reduction of vata and the enhancement of measures for agni and of vegetarian nutrition.
- Depending on the individual constitution and the individual expression of the disease, a personalized knee Yoga posture counseling (asana) and instructions for regular domestic implementation were provided: Knees to chest pose, bridge pose, downward facing dog-pose, half chair pose, hero pose, upside down pose (in Sanskrit: apanasana, dvipada pitham, adhomukhasvanasana, ardha utkatasana, virabhadrasana, viparita karani).
- Ayurvedic dietary supplements, which are customarily available in German pharmacies, were administered. For example, Ashvagandha (botanical name: Withania somnifera Dunal. Linn.) maximum 3 grams twice daily preferably with milk, and yogaraja-guggulu (compound supplement with the main ingredient

Commiphora mukul Hook. ex Stocks) maximum 1.5 grams 3 x daily were prescribed [Bhaisajyaratnavali 2009; Śāraṅgadhara 1984].

- Patients were instructed in self-applied local knee massage (sva-abhyanga) to be done once daily at home.
- Bibliographical and print material was handed out to provide general information about Ayurveda and Ayurvedic treatment options in vata-conditions (e.g. oil enemas, mild purgation, Sanskrit: anuvasana-basti, mrdu-virecana).

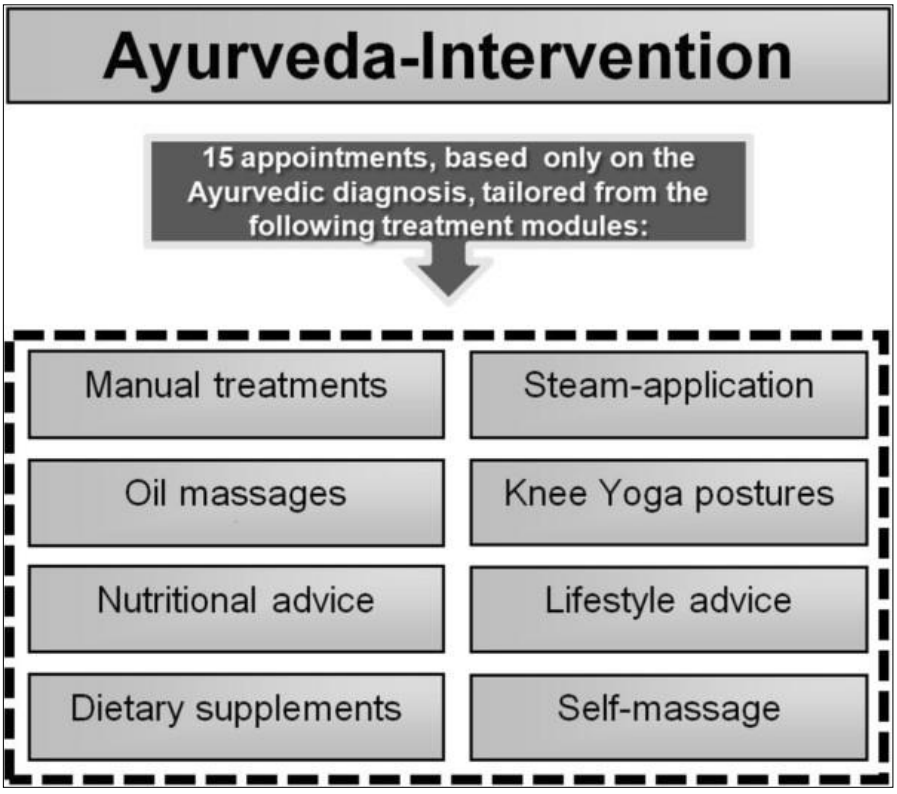

Figure 3.2: Ayurveda-Intervention [Kessler 2018].
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3.7.2 Control-Intervention

The following section is based on Kessler et al. [Kessler 2018]. The authors describe how participants of the conventional group were treated by conventional standard care for OA of the knee [Kessler 2018]. In particular, the standard conventional care was customized to individual requirements according to conventional diagnosis using current international guidelines. In this context a conventional treatment was defined of at most 15 sessions of individualized treatments, which had a maximum duration of 45-50 minutes each [Kessler 2018].

According to Kessler et al. [Kessler 2018] the conventional standard care included:

- personalized instructions for sequences of musculus quadriceps strengthening exercises,
- local physiotherapy including e.g. manual therapy techniques and frictioning.
- occupational therapy,
- counseling for individual knee exercise (knee school),
- personalized nutritional counseling in case of obesity,
- prescription of pharmacological treatment options for acute medication.

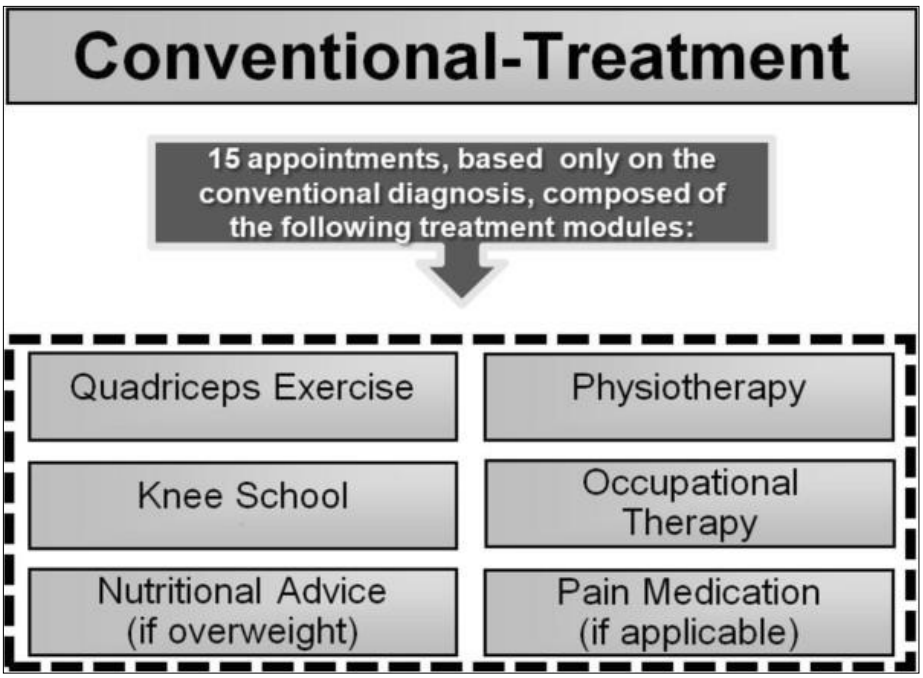

Figure 3.3: Conventional-Treatment [Kessler 2018].
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Kessler et al. describe how participants in both treatment groups had an option to use rescue medication such as paracetamol or topical or oral NSAIDs [Kessler 2018]. In the case of paracetamol, it was defined as no more than "3 g paracetamol per day." Patients were allowed to take "topical or oral NSAIDs" "(e. g. diclofenac-sodium ointment 3 x daily or oral ibuprofen up to a maximum dose of 800 mg per day or equivalent)" in the event of "non-response or intolerance to paracetamol", provided they had previously sought the advice of a study physician. Participants were dissuaded from taking other forms of pain medication. Moreover, patients were ordered to keep a diary of pain medication intake for the duration of the study. [Kessler 2018]

In both the conventional and the Ayurveda group, treatments were performed in 15 sessions over 12 weeks:

- Week 1 to 3: two sessions per week,
- Week 4 to 12: one session per week.

Treatment time was 45 to 50 minutes per session for the conventional guideline care group and 60 to 90 minutes for the Ayurveda group. "Treatment time between groups was not further equalized as a treatment time >50 minutes per session for physio-therapy/exercise would have largely exceeded existing treatment standards for knee OA patients." [Kessler 2018]

3.8 Study Termination Criteria

Different study termination criteria were defined at two different levels: for individual participants and for the whole trial [Witt 2013].

3.8.1 For the Individual Participant

For the individual participant [Witt 2013] described the following study termination criteria:

- intra-individual occurrence of a SAE having a causal relationship to the interventions by the principal investigators;
- withdrawal of the consent to participate in the trial;
- death of a participant;
- missing cooperation and beginning of other treatments of OA of the knee not discussed with the study physician;
- circumstances ruling out a continuation of the study, e.g. a massive worsening of the state of health through a serious illness.

3.8.2 For the Whole Trial

As described in [Witt 2013], every AE and SAE was to be assessed by the investigators with respect to their severity and possible causal relationship to the study interventions. All SAEs were to be reported to the principal investigators by the sub-investigators within 24 hours by telephone, telefax or telegram. In case of occurrence of SAEs, the principal investigators could make the decision to terminate the trial by themselves. The trial was to be terminated if the safety of the therapy was called into question due to the occurrence of SAEs, i.e.:

- inter-individual occurrence of SAEs if considered to be in causal relationships to the interventions by the principal investigators,
- occurrence of serious violations of the study protocol,
- non-adherence to legal or ethical regulations.

3.9 Role of the Funding Source

As described by Witt et al. [Witt 2013], the study was funded by a grant from the Ministry of AYUSH and the Central Council for Research in Ayurvedic Sciences (CCRAS), Delhi, India, which had suggested a randomized trial including a conventional control group for OA of the knee. All other decisions on design, data collection, analysis, interpretation and publication were made independent of the funders.

4. Results

4.1 Study Population

Between October 2010 and January 2014, 329 patients with OA of the knee were contacted, 197 were then assessed for eligibility. Of these, 151 were randomly assigned to the Ayurveda group (n=77) or to the conventional guideline care group (n=74), treated between November 2010 and January 2015 and included in the primary analyses [Kessler 2018]. **Figure** 4.1 shows the study flow of the enrollment and allocation process.

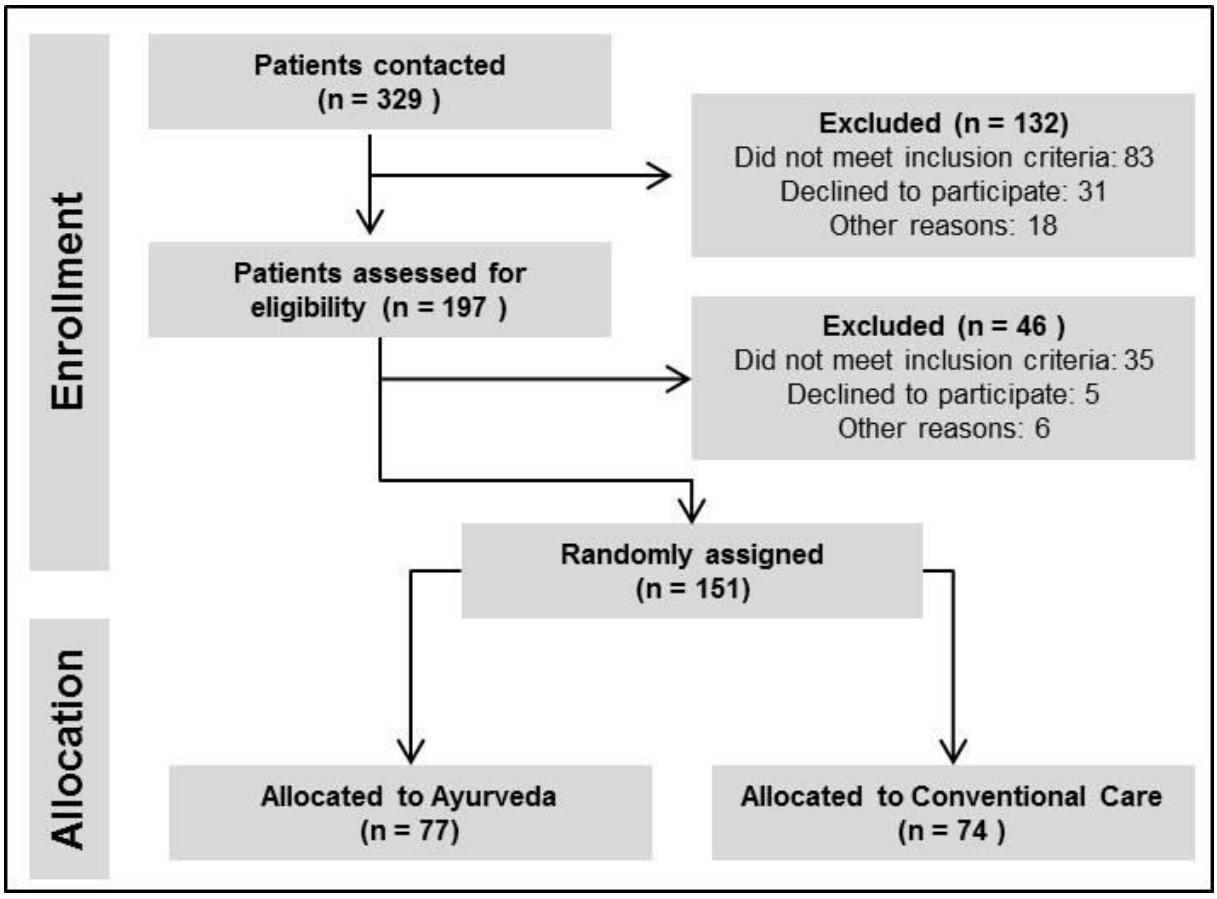

Figure 4.1: Study Flow of the Enrollment and Allocation Process [Kessler 2018]

Patients of both groups were visited after 6 and 12 weeks. Follow-ups were performed after 6 and 12 months. The time flow of study visits and follow-ups are shown in **Figure** 4.2.

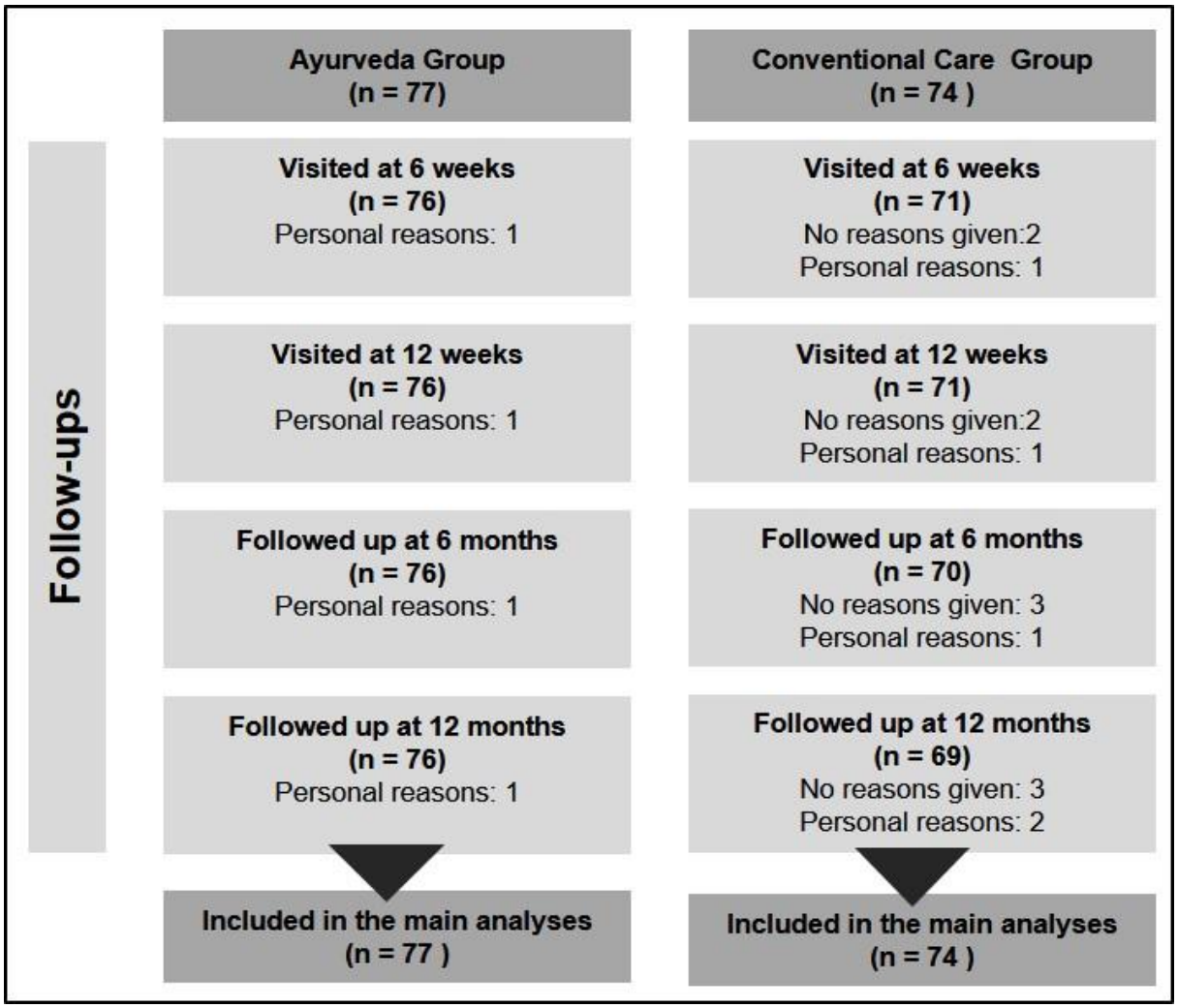

Figure 4.2: Time Flow of study visits and Follow-ups [Kessler 2018]

Values were missing for all outcomes for four patients at 6 and 12 weeks, for five patients at 6 months and for six patients at 12 months. All patients having available baseline data were included in the analyses. Missing outcomes were multiply imputed based on baseline values. No patients were excluded due to missing outcome values [Kessler 2018].

4.2 Baseline Characteristics

4.2.1 Sociodemographic Data and Health Status

Regardless of their group assignment, patients with OA of the knee were 61.2 years old on average (SD = 6.6) at the beginning of the study. The BMI of all patients was 26.1 kg/m² on average, which is age-appropriate. In the age group 55 to 64 years, a BMI of 25 to 29 was acceptable, hence the results were clinically inconspicuous. The number of participants with education ≥10 years of schooling was slightly higher in the Ayurveda Group (56.0 % of the group members) in comparison to the group with conventional treatment (52.7 %). Health condition of all patients with respect to cardiovascular system was unremarkable. The mean blood pressure (systolic/diastolic) was 139.4 mmHg to 85.6 mmHg.

In general, the mean duration of knee pain was 9.4 years for all patients, having 9.7 years in the Ayurveda group and 9.0 years in the conventional group. In some cases, the pain history with respect to OA of the knee was going back up to 18.8 years. However, almost every patient (150 out of 151) had consulted an orthopedic surgeon. The patients had no statistically significant baseline differences. 84.8 % of the patients had consulted a radiologist. Only 10 patients had additional medical care by a neurologist.

Almost all patients (92.7 %) had concomitant diagnoses. In the majority of all cases (43.0 %) patients had five concomitant diagnoses or less. The second highest group with 31.8 % of all patients had 3 to 4 concomitant diagnoses. Overall, baseline characteristics were comparable between the groups. Prior to this study 34 patients (44.2 %) of the Ayurveda group took additional medication for OA of the knee. In comparison 39 patients (52.7 %) from the group with conventional treatment relied on additional medication. An overview of patient baseline data is given in **Table 4.1**.

Table 4.1: Baseline Characteristic – Sociodemographic Data and Health Status [Kessler 2018]

Characteristic Values	All patients (n = 151)	Ayurveda (n = 77)	Conventional (n = 74)
Mean age in years (SD)	**61.2 (6.6)**	**60.9 (6.5)**	**61.5 (6.6)**
Mean Body mass index in kg/m2 (SD)	**26.1 (3.9)**	**25.8 (3.7)**	**26.4 (4.2)**
Education > 10 years of school, in total n	**81 (54.4 %)**	**42 (56.0 %)**	**39 (52.7 %)**
Mean systolic blood pressure, in mmHg (SD)	**139.4 (16.8)**	**137.3 (16.1)**	**141.5 (17.3)**
Mean diastolic blood pressure, in mmHg (SD)	**85.6 (9.4)**	**84.1 (9.6)**	**87.1 (9.1)**
Mean duration of knee pain in years (SD)	**9.4 (8.1)**	**9.7 (9.1)**	**9.0 (7.0)**
Consulting physicians due to OA of the knee, n (%)*			
General practitioner	**87 (57.6 %)**	**47 (61.0 %)**	**40 (54.1 %)**
Orthopedic surgeon	**150 (99.3 %)**	**77 (100 %)**	**73 (98.6 %)**
Other surgeon	**68 (45.0 %)**	**32 (41.6 %)**	**36 (48.6 %)**
Radiologist	**128 (84.8 %)**	**67 (87.0 %)**	**61 (82.4 %)**
Neurologist	**10 (6.6 %)**	**7 (9.1 %)**	**3 (4.1 %)**
Other physicians	**31 (20.5 %)**	**17 (22.1 %)**	**14 (18.9 %)**
Patients with concomitant diagnoses (CD), n (%)	**140 (92.7 %)**	**71 (92.2 %)**	**69 (93.2 %)**
Mean number of CD (SD)	**4.3 (2.5)**	**4.4 (2.6)**	**4.1 (2.4)**
Patients with 1-2 CD, n (%)	**27 (17.9 %)**	**13 (16.9 %)**	**14 (18.9 %)**
Patients with 3-4 CD, n (%)	**48 (31.8 %)**	**22 (28.6 %)**	**26 (35.1 %)**
Patients with ≥ 5 CD, n (%)	**65 (43.0 %)**	**36 (46.8 %)**	**29 (39.2 %)**
Medication intake for knee OA, n (%)	**73 (48.3 %)**	**34 (44.2 %)**	**39 (52.7 %)**

Abbreviations

* = multiple answers possible; SD = Standard Deviation; CD = Concomitant Diseases;
OA = Osteoarthritis

4.2.2 Main Outcomes

The mean WOMAC Index was measured at 92.6 (SD = 42.2) for all patients. It was higher in the conventional group (94.2, SD = 44.4) than in the Ayurveda group (91.1, SD = 40.3). Furthermore, the WOMAC Index is divided into the three subscales: pain, stiffness and function. There were no statistically significant baseline differences for any of the three subscales. Nevertheless, measurements for the conventional group were slightly higher than for the Ayurveda group for all three subscales.

Similarly, the mean Pain Disability Index (PDI) of the conventional group was slightly higher (25.1, SD = 12.1) than in the Ayurveda Group (22.6, SD = 10.6). Conversely, both affective and sensory measurements of the Pain Experience Scale (SES) were slightly higher in the Ayurveda group than the group of the conventional treatment.

The Profile of Mood States (POMS), which contains depression, fatigue, vigor and anger, displayed no significant differences between the two groups. However, the situation was different with the values on SF-36 (Short Form-36). While the physical component summary was not significantly higher for either group, the mental component summary in the conventional group (52.4, SD = 10.5) was slightly higher than in the Ayurveda group (50.4, SD = 12.1).

The Numeric Rating Scale (NRS) contains pain at rest, pain during movement and everyday bothersomeness through pain. In this context, a higher score means greater pain experienced. In addition to this, a fourth subscale, sleep quality, was introduced, which indicates better quality with higher scores. Pain at rest values (3.4, SD = 2.3) were identical in both groups. As for the remaining parts of the NRS, the values of the conventional group were consistently higher than in the Ayurveda group.

Table 4.2 shows an overview of the baseline data, representing the initial values of parameters monitored throughout the study.

Table 4.2: Baseline Data for Main Outcomes Status [Kessler 2018]

Pain Indices	All patients (n = 151)	Ayurveda (n = 77)	Conventional (n = 74)
WOMAC, mean (SD)			
Index	**92.6 (42.2)**	**91.1 (40.3)**	**94.2 (44.4)**
Pain subscale	**19.3 (8.5)**	**19.0 (8.1)**	**19.6 (9.0)**
Stiffness subscale	**9.9 (4.7)**	**9.8 (4.7)**	**10.1 (4.7)**
Function subscale	**63.4 (31.8)**	**62.3 (30.6)**	**64.5 (33.1)**
PDI, mean (SD)	**23.8 (11.4)**	**22.6 (10.6)**	**25.1 (12.1)**
SES, mean (SD)			
Affective	**27.1 (8.2)**	**27.3 (8.8)**	**26.9 (7.6)**
Sensory	**18.2 (5.7)**	**18.3 (5.6)**	**18.1 (5.8)**
POMS, mean (SD)			
Depression factor	**1.5 (0.9)**	**1.5 (1.0)**	**1.4 (0.9)**
Fatigue factor	**1.8 (0.9)**	**1.8 (0.9)**	**1.8 (0.9)**
Vigor factor	**2.0 (0.7)**	**2.0 (0.6)**	**2.0 (0.7)**
Anger factor	**1.7 (0.9)**	**1.8 (0.9)**	**1.7 (0.8)**
SF-36, mean (SD)			
Physical component summary	**33.2 (7.7)**	**33.4 (7.4)**	**33.0 (8.1)**
Mental component summary	**51.3 (11.3)**	**50.4 (12.1)**	**52.3 (10.5)**
NRS (11-point 0-10), mean (SD)			
Pain at rest	**3.4 (2.3)**	**3.4 (2.3)**	**3.4 (2.3)**
Pain during movement	**5.6 (1.9)**	**5.4 (2.0)**	**5.9 (1.7)**
Everyday bothersomeness through pain	**5.3 (2.0)**	**5.1 (2.1)**	**5.6 (1.9)**
Sleep quality	**5.6 (2.5)**	**5.2 (2.5)**	**6.0 (2.5)**

Abbreviations

* = multiple answers possible; SD = Standard Deviation; CD = Concomitant Diseases;
WOMAC = Western Ontario and McMaster University Osteoarthritis Index;
PDI = Pain Disability Index; SES = Pain Experience Scale; POMS = Profile of Mood States;
SF-36 = Short Form-36; NRS = Numeric Rating Scale

4.2.3 Patients' and Physicians' Expectations

Patients documented their expectations for treatment outcome at baseline. Both patients and physicians had higher expectations for Ayurveda than for conventional care (**Table 4.3**). Furthermore, the physicians' expectations of the conventional therapy were lower than those of the patients. This was taken into account in the sensitivity analyses (**chapter 4.3**).

Table 4.3: Patients' and Physicians' Expectations at Baseline [Kessler 2018]

Characteristic Values according to Likert scale (7-point, 0-6), mean (SD)	All patients (n = 151)	Ayurveda (n = 77)	Conventional (n = 74)
Patients´ expectations of Ayurveda therapy			
Reduction of OA complaints	**4.8 (1.1)**	**4.8 (1.1)**	**4.8 (1.0)**
Overall effectiveness	**4.7 (1.2)**	**4.6 (1.2)**	**4.9 (1.1)**
Comprehensibility	**4.6 (1.3)**	**4.6 (1.3)**	**4.6 (1.3)**
Patients´ expectations of conventional therapy			
Reduction of OA complaints	**3.8 (1.3)**	**3.7 (1.3)**	**3.9 (1.4)**
Overall effectiveness	**3.7 (1.2)**	**3.4 (1.1)**	**4.0 (1.2)**
Comprehensibility	**4.1 (1.4)**	**4.0 (1.3)**	**4.2 (1.4)**
Physicians´ expectations of Ayurveda therapy			
Reduction of OA complaints	**5.0 (1.0)**	**5.1 (1.0)**	**5.0 (1.0)**
Overall effectiveness	**4.5 (0.9)**	**4.5 (1.0)**	**4.5 (0.9)**
Comprehensibility	**4.7 (1.1)**	**4.7 (1.1)**	**4.7 (1.0)**
Physicians´ expectations of conventional therapy			
Reduction of OA complaints	**3.5 (0.9)**	**3.4 (1.0)**	**3.5 (0.8)**
Overall effectiveness	**3.0 (0.9)**	**3.0 (0.9)**	**3.0 (0.8)**
Comprehensibility	**3.8 (1.1)**	**3.7 (1.1)**	**3.8 (1.1)**

Abbreviations

SD = Standard Deviation; OA = Osteoarthritis

4.3 Primary Outcomes

Main results of the primary outcomes are summarized in **Table 4.4**, which were used for graphical interpretation. The graphs in **Figure 4.3**, **Figure 4.4**, **Figure 4.5** and **Figure 4.6** show relevant excerpts from this table to draw general statements. The WOMAC Index were assessed for a period of 12 months after the end of the intervention. As mentioned above, the study assessed outcomes at 0, 6, 12 weeks and follow-ups after 6 and 12 months.

According to **Table 4.4**, patients in the Ayurveda group started with slightly lower mean (12 weeks) the results improved continuously for both groups. The improvements in score points were higher in the first half of the active treatment period than in the second half. As expected, the effects of the treatments were slightly reduced during the follow-up period. Statistically significant and clinically relevant effects could be observed throughout all time-periods and for both groups. However, the magnitude of the observed changes at any time was larger in the Ayurveda group.

While there is a clear improvement in the conventional group from 94.2 to 62.2 points after 12 weeks of treatment, the improvement in the Ayurveda group is even bigger, from 91.1 down to 30.0 points. Even 9 months after the last treatment, only slight deterioration occurred in both groups. For the Ayurveda group the last measured value after 12 months is 43.0 points and in the conventional group it is 69.6 points. It is worth mentioning that after completing the treatments, the difference in the values between the Ayurveda group and the conventional group is significant and it remained stable during the follow-ups.

The between-group difference (baseline to 12 weeks) shows that there was a significant difference between the two groups ($p < 0.001$). Using Cohen's d-algorithm, the results reveal an effect size of 0.68 [95 % CI: 0.35; 1.01], which indicates a medium effect size for WOMAC Index. Hence, these results are clinically relevant. It is worth noting that within-group changes in the conventional group were also statistically significant, indicating beneficial effects in both groups.

Table 4.4: Primary Outcomes: WOMAC Index and WOMAC Subscales [Kessler 2018]

	Time Point				**Within Group Differences (Baseline to 12 weeks)**			**Between Group Differences (Baseline to 12 weeks)**	
	Week 6 Mean [95 % CI]	**Week 12 Mean [95 % CI]**	**Month 6 Mean [95 % CI]**	**Month 12 Mean [95 % CI]**	**Δ Mean [95 % CI]**	**Effect Size [95 % CI]**	**p-Value**	**Effect Size [95 % CI]**	**p-Value**
WOMAC Index									
Ayurveda	**49.6** [41.9; 57.3]	**30.0** [24.0; 36.1]	**36.3** [28.1; 44.4]	**43.0** [34.3; 51.7]	**61.0** [52.4; 69.6]	**1.78** [1.41; 2.16]	< 0.001	**0.68** [0.35; 1.01]	< 0.001
Conventional	**74.5** [65.7; 83.3]	**62.2** [52.4; 72.0]	**66.3** [56.9; 75.7]	**69.6** [59.9; 79.2]	**32.0** [21.4; 42.6]	**0.73** [0.46; 1.00]	< 0.001		
Pain (subscale)									
Ayurveda	**10.4** [8.8; 12.0]	**6.2** [4.8; 7.6]	**7.2** [5.4; 8.9]	**7.9** [6.3; 9.6]	**12.8** [10.8; 14.8]	**1.77** [1.37; 2.17]	< 0.001	**0.64** [0.32; 0.97]	< 0.001
Conventional	**15.9** [14.0; 17.9]	**13.0** [10.7; 15.2]	**13.7** [11.6; 15.8]	**14.0** [11.9; 16.1]	**6.7** [4.4; 8.9]	**0.70** [0.44; 0.97]	< 0.001		
Stiffness (subscale)									
Ayurveda	**5.4** [4.4; 6.4]	**3.6** [2.8; 4.4]	**4.1** [3.2; 4.9]	**4.8** [3.8; 5.8]	**6.2** [5.2; 7.2]	**1.51** [1.17; 1.84]	< 0.001	**0.63** [0.30; 0.95]	< 0.001
Conventional	**7.4** [6.4; 8.4]	**6.7** [5.7; 7.7]	**6.8** [5.8; 7.8]	**7.1** [6.0; 8.1]	**3.4** [2.3; 4.4]	**0.74** [0.47; 1.00]	< 0.001		
Function (subscale)									
Ayurveda	**33.8** [28.2; 39.5]	**20.2** [16.0; 24.5]	**25.0** [19.2; 30.8]	**30.3** [23.8; 36.8]	**42.0** [35.7; 48.4]	**1.65** [1.29; 2.00]	< 0.001	**0.64** [0.32; 0.97]	< 0.001
Conventional	**51.2** [44.9; 57.5]	**42.6** [35.6; 49.5]	**45.8** [39.1; 52.5]	**48.5** [41.5; 55.5]	**22.0** [14.3; 29.7]	**0.69** [0.42; 0.96]	< 0.001		

Abbreviations: WOMAC = Western Ontario and McMaster University Osteoarthritis Index; CI = Confidence Interval

Based on the changes in the WOMAC Index over time, it can be seen that there are significant improvements for both groups, Ayurveda and conventional, with enduring, sustainable effects. The course of the curves is similar for both groups, with a larger improvement in the Ayurveda group (**Figure** 4.3).

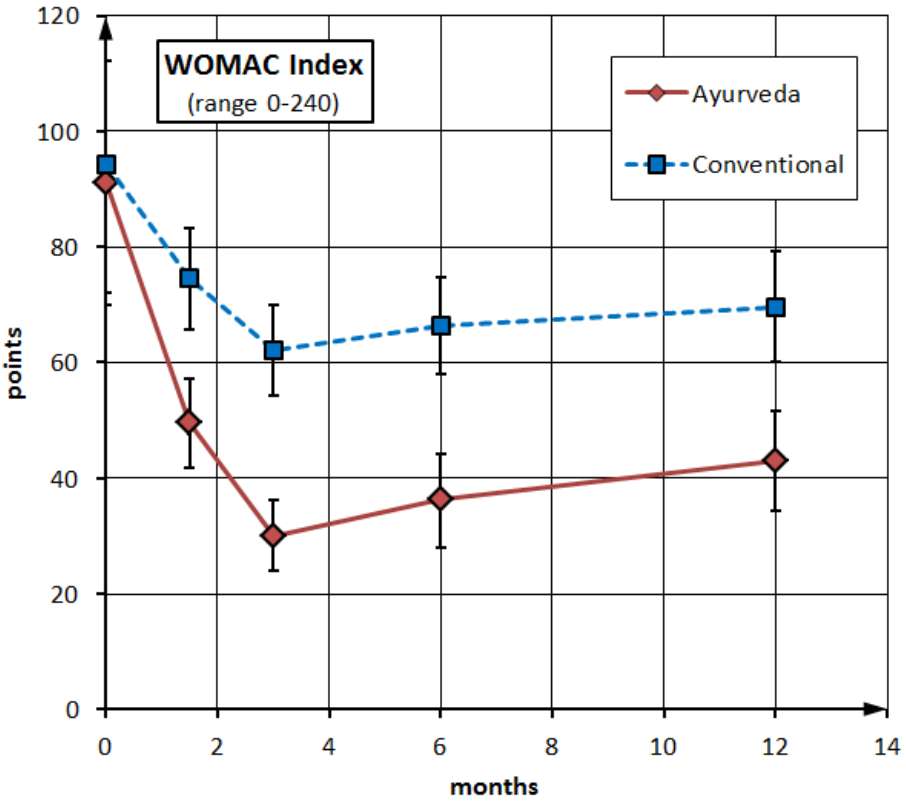

Figure 4.3: WOMAC Index

Sensitivity Analyses

Analysis showed that findings were robust for sensitivity analyses. Interaction tests did reveal significant relationships and associations between study outcome and baseline data and between study outcomes and expectation of the patient for the treatment (**Table 4.3**). For the WOMAC Index and for each WOMAC subscale similar significant differences between the two randomized groups ($p<0.001$) were observed in a treatment expectation adjusted model according to ANCOVA (**chapter 3.5.3**). The proportion of treatment responders was 93.5 % for Ayurveda, and 60.8 % for conventional guideline care (Chi-Square: 21.24; $p < 0.001$). [Kessler 2018]

WOMAC Subscales

As **Table 4.4** indicates, the effect size according to Cohen's d the WOMAC subscales pain, stiffness and function still remained ≥ 0.63 and the p-Value was still < 0.001. The WOMAC subscale results are also clinically relevant. All changes within each WOMAC subscale showed better results in the Ayurveda group compared to the conventional treatment as can be seen in **Figure** 4.4, **Figure** 4.5 and **Figure** 4.6.

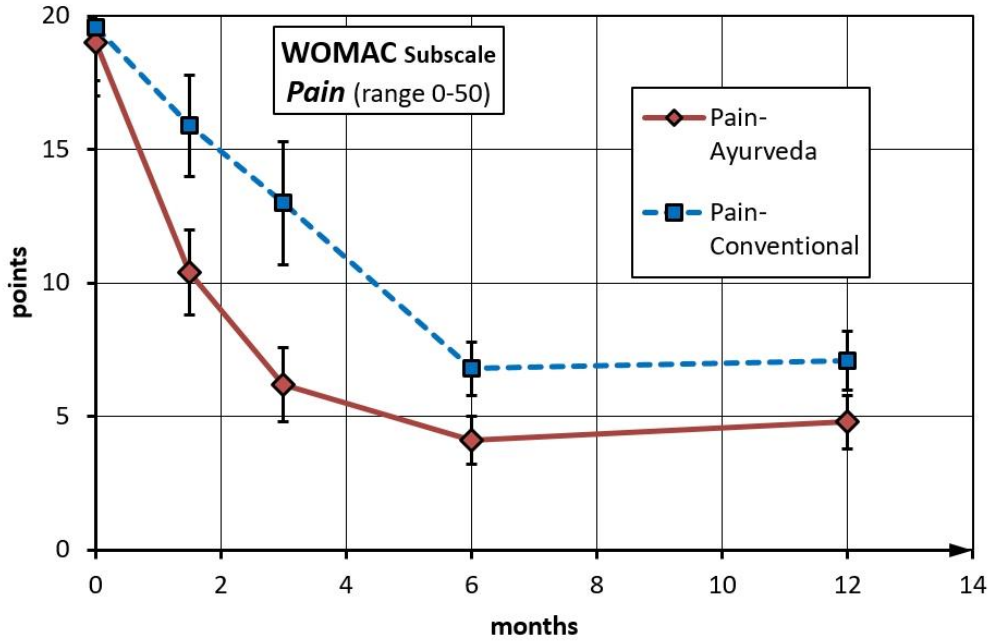

Figure 4.4: WOMAC Subscale – Pain

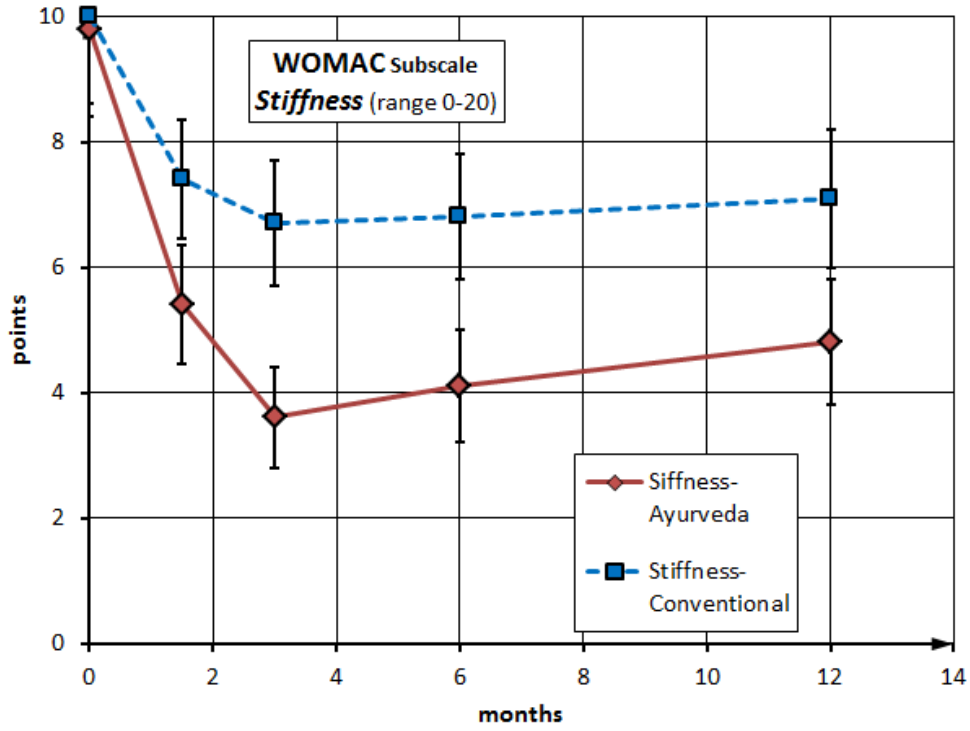

Figure 4.5: WOMAC Subscale – Stiffness

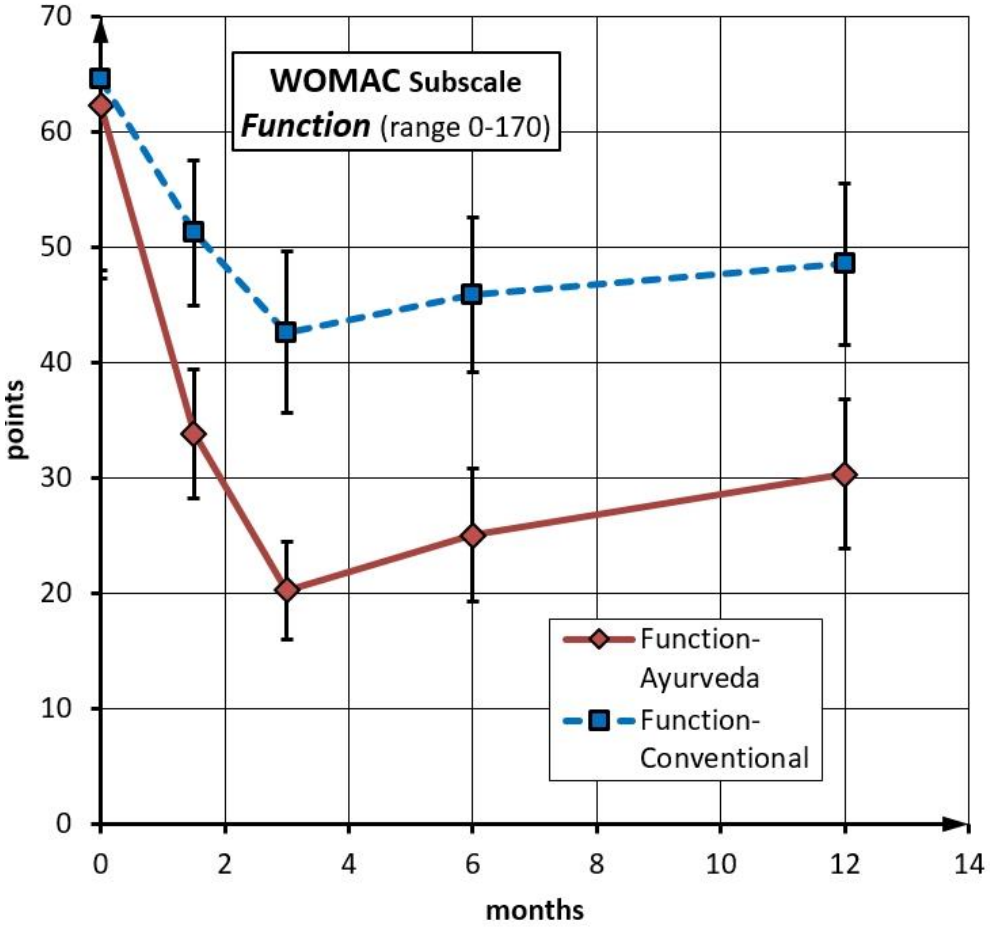

Figure 4.6: WOMAC Subscale – Function

4.4 Secondary Outcomes

Main results of the secondary outcomes are summarized in **Table 4.5**, which were used as a starting point for a graphic evaluation. The graphs in **Figure 4.7**, **Figure 4.8** and **Figure** 4.9 show relevant excerpts from this table to draw general statements.

Figure 4.7 shows that the Pain Disability Index (PDI) mainly followed the course of the main WOMAC Index. The values displayed for each group could be clearly differentiated. Standard deviations (SD) did not overlap. Up to week 12, a significant improvement was achieved, i.e. the score points were decreasing in both groups. This was followed by a slight increase of values in both groups until the end of the study. However, the total improvement, which is defined as the difference between baseline and 12 months, was still significant.

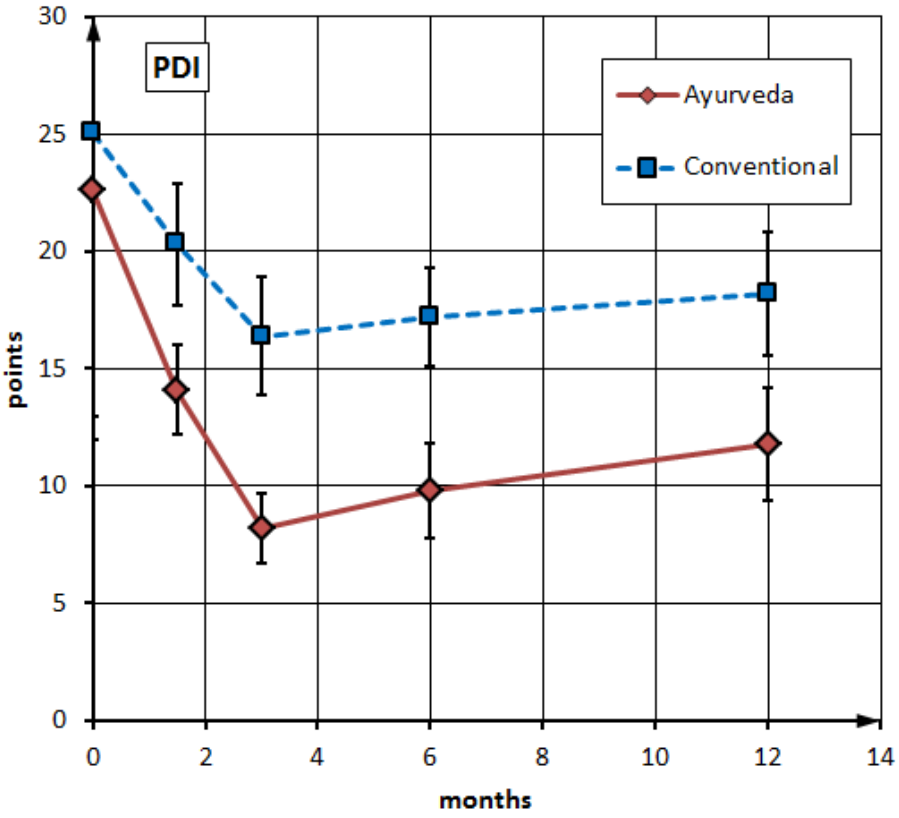

Figure 4.7: Secondary Outcomes – Pain Disability Index (PDI)

Table 4.5: Secondary Outcomes [Kessler 2018]

	Ayurveda Group (SD)				Conventional Group (SD)				Between Groups Baseline Week 12	
	Week 6	**Week 12**	**Month 6**	**Month 12**	**Week 6**	**Week 12**	**Month 6**	**Month 12**	**Mean Δ (95 % CI)**	**p-Value**
PDI	14.1 (12.2; 16.1)	8.2 (6.7; 9.7)	9.8 (7.8; 11.9)	11.8 (9,4; 14,2)	20.3 (17.7; 22.9)	16.4 (13.9; 18.9)	17.2 (15.1; 19.4)	18.2 (15.6; 20.9)	5.8 (2.1; 9.5)	0.002
SES										
Affective	21.9 (20.1; 23.7)	18.3 (16.9; 19.8)	18.7 (17.1; 20.4)	19.0 (17.7; 20.3)	23.9 (22.3; 25.5)	21.5 (19.8; 23.2)	21.8 (20.2; 23.3)	21.2 (19.8; 22.6)	3.1 (1.0; 6.2)	0.007
Sensory	15.7 (14.7; 16.7)	13.5 (12.4; 14.5)	13.6 (12.5; 14.8)	14.2 (13.0; 15.4)	15.8 (14.8; 16.9)	15.0 (14.0; 16.1)	15.2 (14.2; 16.2)	15.3 (14.3; 16.3)	1.8 (-0.1; 3.7)	0.060
POMS										
Depress.	1.1 (1.0; 1.3)	1.1 (0.9; 1.3)	1.3 (1.1; 1.6)	1.5 (1.2; 1.7)	1.4 (1.1; 1.6)	1.2 (1.0; 1.4)	1.4 (1.2; 1.6)	1.3 (1.1; 1.5)	0.2 (-0.1; 0.4)	0.190
Fatigue	1.6 (1.4; 1.8)	1.5 (1.3; 1.7)	1.7 (1.5; 1.9)	1.9 (1.6; 2.1)	1.9 (1.7; 2.1)	1.7 (1.5; 1.9)	1.8 (1.6; 2.0)	1.8 (1.6; 2.0)	0.2 (0.0; 0.5)	0.089
Vigor	1.8 (1.7; 2.0)	1.8 (1.7; 2.0)	1.9 (1.8; 2.1)	2.0 (1.9; 2.2)	1.9 (1.8; 2.1)	1.9 (1.8; 2.0)	1.9 (1.7; 2.0)	2.0 (1.8; 2.1)	0.1 (-0.1; 0.3)	0.502
Anger	1.6 (1.5; 1.8)	1.5 (1.4; 1.7)	1.7 (1.5; 2.0)	1.7 (1.5; 1.9)	1.5 (1.3; 1.7)	1.6 (1.4; 1.7)	1.6 (1.5; 1.8)	1.7 (1.5; 1.9)	0.2 (-0.1; 0.4)	0.217
SF-36										
Subscales										
PCS	39.5 (37.7; 41.4)	44.9 (43.1; 46.7)	43.0 (40.9; 45,2)	41.7 (39.5; 44.0)	36.1 (34.1; 38.1)	37.9 (35.7; 40.1)	37.1 (35.0; 39.2)	37.1 (35.0; 39.1)	-6.6 (-9.3; -3.9)	< 0.001
MCS	52.8 (50.5; 55.0)	53.7 (51.7; 55.7)	53.0 (51,1; 55,0)	52.5 (50.5; 54.4)	52.7 (50.1; 55.3)	53.9 (51.7; 56.1)	54.1 (52.0; 56.1)	54.0 (51.7; 56.2)	-1.7 (-5.1; 1.6)	0.308
NRS (11-p)										
Pain Rest	1.7 (1.3; 2.1)	1.0 (0.7; 1.3)	1.2 (0.8; 1.5)	1.3 (1.0; 1.7)	2.5 (2.1; 2.9)	2.3 (1.7; 2.8)	2.2 (1.7; 2.6)	2.1 (1.7; 2.5)	1.3 (0.5; 2.0)	0.001
Pain Mov.	3.4 (3.0; 3.9)	2.5 (2.0; 2.9)	2.6 (2.1; 3.0)	2.7 (2.2; 3.2)	4.7 (4.2; 5.1)	3.9 (3.4; 4.5)	4.0 (3.5; 4.5)	4.2 (3.7; 4.7)	0.9 (0.2; 1.6)	0.018
Pain Both.	3.2 (2.8; 3.7)	2.0 (1.6; 2.3)	2.4 (1.9; 2.8)	2.5 (2.0; 3.0)	4.5 (4.0; 5.0)	3.8 (3.2; 4.4)	3.8 (3.3; 4.3)	4.1 (3.6; 4.7)	1.4 (0.7;2.1)	< 0.001
Sleep	6.0 (5.5; 6.6)	6.4 (5.8; 7.0)	6.4 (5.8; 7.0)	6.0 (5.4; 6.5)	5.8 (5.2; 6.3)	6.5 (6.0; 7.1)	5.8 (5.2; 6.3)	6.0 (5.4; 6.6)	-0.6 (-1.5;0.2)	0.146

Abbreviations: CI = Confidence Interval; PDI = Pain disability index; SES = Pain experience scale; POMS = Profile of mood states; SF-36 = Short form 36; NRS = Numeric rating scale

Comparable to the outcomes of the WOMAC Index, the difference in PDI values after week 12 between both groups remained consistent to a great extent. The graph indicates that there was a significant difference in the patients' results according to the treatment. The comparison of the difference between baseline and week 12 shows that the p-value ($p = 0.002$) stayed under the level of significance of $\alpha = 0.05$. The values of both groups were quite close to each other, with a small maximum score range for PDI of 55 points. However, null hypothesis did not lose its validity, but the results, i.e. the difference in values, were not significant.

Furthermore, **Table 4.5** illustrates the Pain Experience Scale (SES), which is mainly a measurement of the patients' subjectively perceived pain. Focusing on the affective measurement first, it can be seen that starting from baseline values with 27.3 (SD = 8.8) for the Ayurveda group and 26.9 (SD = 7.6) for the conventional group, a considerable improvement was achieved in both treatments. After 12 weeks, the values decreased down to 18.3 (SD = 2.9) for the Ayurveda group and 21.5 (SD = 3.4) for the conventional group. It is worth mentioning that the improvements in both groups had a persistent effect. Even after 12 months, values remained, stable with 19.0 (SD = 3.3) for the Ayurveda group and 21.8 (SD = 2.8) for the conventional group. Since the p-value was 0.007, which is defined as the difference between groups in week 12, the differentiation did not have the highest significance. In summary, the analysis of the SES affective measurements shows that both therapies led to a considerable improvement of the pain-situation. However, the p-value suggested that neither of the therapies stands out in particular. A similar tendency could be observed for the SES sensory measurement. In this case the p-value was even higher ($p = 0.06$).

Looking at the POMS results in **Table 4.5** it is evident that no values (depression, fatigue, vigor and anger) passed the level of significance α. All p-values were so high that null hypothesis has to be accepted as valid for POMS. It shows that there was no significant difference in treatment, Ayurveda nor conventional, when it came to POMS values. Furthermore, it clearly shows that Ayurveda treatment was not a psychomental placebo-medication, but rather indicates that there were effects on the patients' condition. This becomes more evident when comparing physical components, having significant results, to mental components with non-significant results.

However, the situation was different with the outcome of the SF-36 subscale PCS (Physical Component Score). **Figure 4.8** shows the graphs for both treatments. A higher score shows better mobility. In this case the scores were higher with Ayurveda in comparison to conventional treatment. Even in this case, the course of the graphs follows the same pattern as on the WOMAC Index. For the active time of treatment, a rapid improvement in values was observable. With the end of treatment, after week 12, all values decreased slightly. However, a positive effect still remained after 12 months. **Figure 4.8** also shows a significant difference between results of Ayurveda and conventional treatment: Ayurveda results tend to be better. The difference between groups remained even after 12 months. Values were stable and the standard deviations bars do not overlap. The p-value was below 0.001, hence results are deemed to be significant.

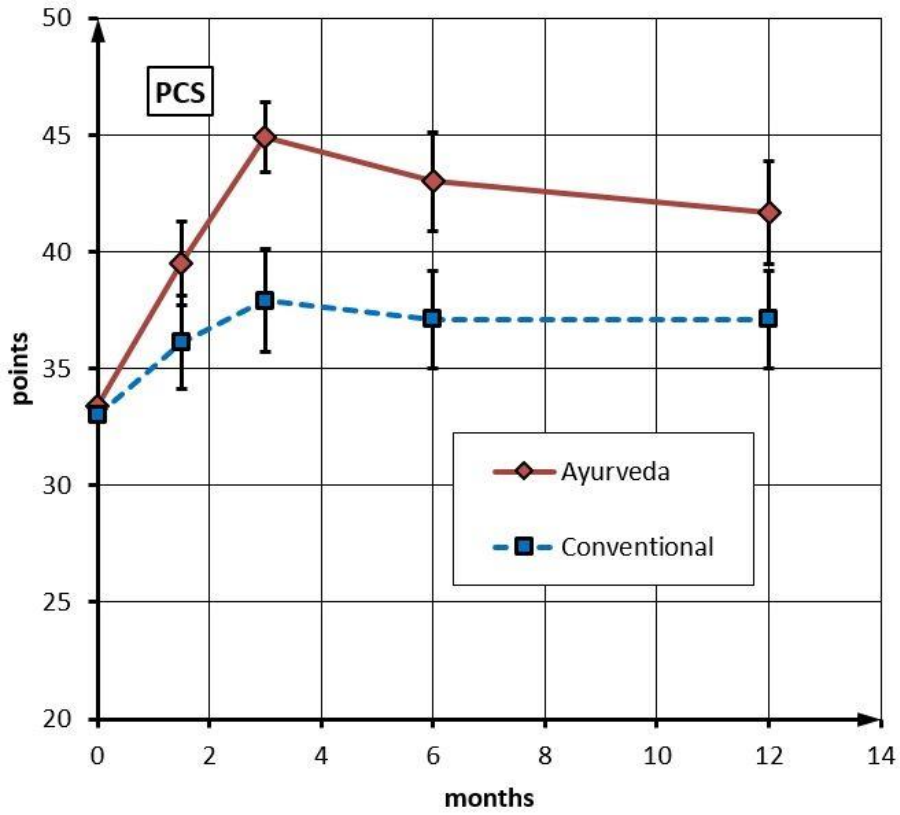

Figure 4.8: Secondary Outcomes – Physical Component Score (PCS)

The SF-36 subscale MCS, which is given in **Figure** 4.9 stands in contrast to the latter outcomes. The graph underlines how close the results of both groups were to each other. The standard deviations (SDs) overlap at every single point of the graph. Hence, the alternative hypothesis is not valid: With respect to the SF-36 subscale MCS, neither

Ayurveda nor conventional treatment tends to have a better or worse effect on the patients' condition. This conclusion is consistent with the calculated p-values ($p = 0.308$). Furthermore, a value of $p > 0.05$ signifies that the evidence is not adequate to reject the null hypothesis. In addition, **Figure 4.8** and **Figure 4.9** show that physical and more mental outcomes in the Ayurveda group improved during the intervention, whereas after the end of the intervention, mental improvements decreased, but physical improvements remained.

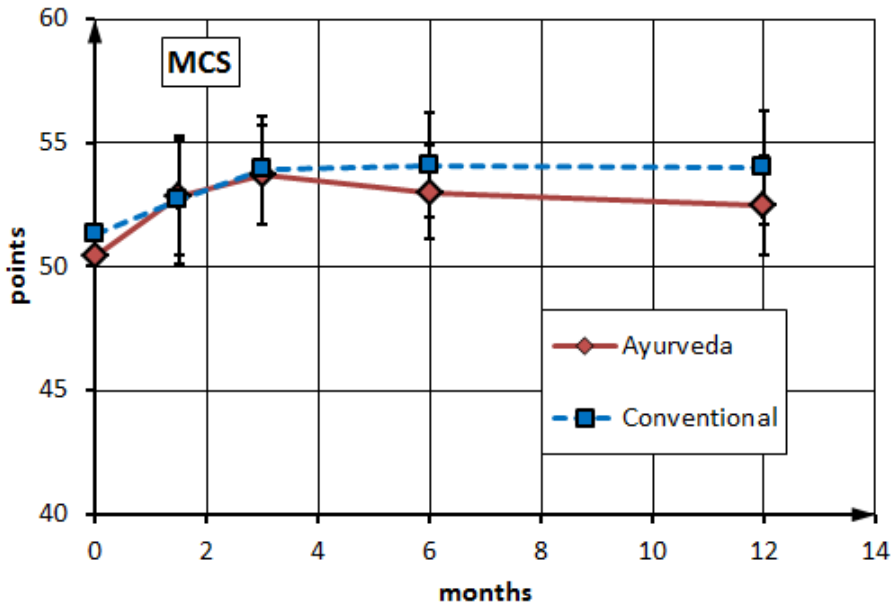

Figure 4.9: Secondary Outcomes – SF-36 Subscale – MCS

The results of the Numeric Rating Scale (NRS) can be taken from **Table 4.5**. The items pain at rest, pain during movement, everyday bothersomeness through pain show improvements of patients' condition regardless of the treatment provided. In all cases, the Ayurveda treatments show even lower values and better results. The differences between the two groups are mainly significant: $p = 0.001$ for 'pain at rest', $p = 0.018$ for pain during movement and $p < 0.001$ for everyday bothersomeness through pain. However, neither of the treatments had any impact on sleep quality. There was no significant difference according to the results of the two treatments for this item.

Generally speaking, changes within each WOMAC subscale and all other secondary outcomes were in favor of Ayurveda at week 12. Similar findings could be observed at months 6 and 12, with the exception of POMS scales and the Mental Component Score (MCS) of the SF-36 subscale (**Figure** 4.9; **Table 4.5**).

4.5 Safety

The following paragraph is based on the paper of Kessler et al. [Kessler 2018]. The authors describe how 137 AEs on 73 patients occurred during the duration of the intervention. AEs were caused by the locomotor system (n = 88), the skin (n = 9) or other reasons (n = 40). In the Ayurveda group 46 participants (59.7 % of patients) and 27 participants in the conventional group (36.5 % of patients) had at least one AE. This resulted in "a mean of 1.2 ± 1.3 AEs (range 0-6)" for Ayurveda patients and a mean of "0.6 ± 1.0 AEs (range 0-5)" for patients of the conventional group. Hence, in the Ayurveda group "the difference in proportion (p = 0.004)" and the number of AEs (p = 0.002) were statistically greater. There were no "clinically relevant diseases" that were linked to the "intervention-related AEs". None of the AEs had to be treated in the hospital. Kessler also suggests that a total of 4 SAEs (i.e. "fracture of radius, cholecystectomy, major depression episode, erysipelas") in 4 patients (three from the Ayurveda group and one from the conventional group) arose. However, none of the SAEs were found to be associated to the study interventions [Kessler 2018].

5. Discussion

5.1 Summary of Results

The present study examined the effectiveness of complex Ayurveda treatment compared to conventional care treatment in patients with knee OA by means of a randomized controlled intervention study. The results showed that both treatments are suitable to achieve significant and clinically relevant improvements in disease-specific symptom reduction. In both groups, effects lasted over 12 months and suggest sustainability. However, the treatment effects in the Ayurveda group were larger in comparison to the conventional treatment group, with significant differences between the groups. For the primary outcome and several of the secondary outcomes, group differences were statistically significant. Within 12 weeks of treatment, the greatest improvements compared to the control group were observed on the WOMAC subscale function with an effect size ≥ 0.63 and p-value < 0.001. For most secondary outcomes, the differences between the groups were also significant, with better results in the Ayurveda group, but not as dominant as for the primary outcome. These included PDI (Pain Disability Index), the SF-36 subscale PCS and a number of NRSs. POMS subscales (depression factor, vigor factor, anger factor) and the SF-36 subscale MCS (Mental Component Score) did not show significant group differences be found.

5.2 Study Population

Surveys have revealed that the prevalence of OA of the knee increases rapidly around age 50 and levels off after age 70 [Oliveria 1995]. Regardless of their group assignment, this study shows similar figures: Participants with OA of the knee were 61.2 years on average at the beginning of the study. Surveys showed furthermore that the risk of OA of the knee rises to 60 % with BMI of 30. In the present study, participants of the Ayurveda group had an average BMI of 25.8 and the conventional group had an average BMI of 26.4. Therefore, the BMI was clinically unremarkable and no need was seen to measure it again at the end of the trial. The health condition of all patients with respect to the cardiovascular system was also unremarkable. The mean blood pressure (systolic/ diastolic) was 139.4 mmHg to 85.6 mmHg.

5.3 Results

The participants showed no statistically significant baseline differences, therefore, it was possible to compare the results between the two groups. Firstly, this study shows that both treatments led mainly to an improvement of patients' conditions. Secondly, the changes of the global WOMAC Index and all WOMAC subscales from baseline to 12 weeks were more in favor of the Ayurveda group. The comparison of the between-group differences showed a clear distinction with statistical significance ($p < 0.001$). In all cases the effect sizes were > 0.68 [95 % CI: 0.35; 1.01] according to Cohen's d-algorithm. Hence, all results were clinically relevant. Notably, within-group changes in the conventional group were also statistically significant, indicating beneficial effects in both groups. Upon closer examination of the WOMAC subscales it becomes evident that the driving factor for the Ayurveda group's significantly higher WOMAC Index values after 12 weeks is the WOMAC subscale function (**Figure 4.6**). Furthermore, the Ayurveda group displayed better values at months 6 and 12 for all primary and secondary outcomes.

Changes within secondary outcomes were mainly in favor of Ayurveda after 12 weeks of treatment. The POMS-results (Profile of Mood States) were one of the exceptions. The findings in subscale fatigue factor might indicate that there is a certain significance in the between-group difference ($p = 0{,}089$) after 12 weeks of treatment, but the improvements were within the range of the standard deviations of the initial baseline data 1.8 (SD = 0.9) for both treatments. The same goes for all other POMS subscales (depression factor, vigor factor, anger factor), but with the difference that there is no significant distinction in between-group results ($p > 0.190$), thus the null hypothesis must be confirmed. The broad distribution of the baseline data for POMS analysis is a possible indication of patients' heterogeneity with regard to the psychological component and distinct mood states.

In addition, the Mental Component Score (MCS) within the SF-36 analysis seemed to be an exception to the general progression mentioned above as well. Here, too, baseline data showed a larger standard deviation, which might be a possible indication of patients' heterogeneity: 50.4 with SD = 12.1 for Ayurveda group and 52.3 with SD = 10.5 for conventional group. The improvement to 53.7 for Ayurveda group and 53.9 for conventional group in week 12 was within the range of statistical variance.

However, in the Ayurveda group physical and mental outcomes improved during the intervention, whereas afterwards mental improvements decreased again, but physical improvements remained (**Table 4.5**) [Kessler 2018].

Looking at the progression of sleep quality within the Numeric Rating Scale (NRS), it is remarkable that only a small improvement could be achieved. The changes described could be interpreted as clinically relevant, but the between-group difference was not of significance after 12 weeks of treatment. Thus, neither of the used therapies is better or worse suited to improve sleep quality in particular.

It is noticeable that while the treatment lasted 12 weeks only, beneficial effects persisted up to 12 months [Kessler 2018]. In the Ayurveda group this might have been particularly due to the integration of elements of active self-care into the individualized therapeutic schemes, including self-empowerment via nutritional advice, lifestyle counseling and knee yoga postures [Kessler 2018].

5.4 Strengths and Limitations

5.4.1 Strengths

When evaluating the study using the criteria proposed by Jadad et al. [Jadad 1996], one comes to the conclusion that this was a randomized, controlled, open-label clinical trial with a high study methodology. Both the Ayurvedic as well as the conventional care approach were devised to implement best practices for each group. Ayurvedic literature for the Ayurveda group and prevailing guidelines for the conventional group were utilized [Kessler 2018]. Other sources, such as Experts in both Ayurveda and orthopedics from three different countries (India, Germany and Italy) used the Delphi consensus method for designing the specific interventions. Furthermore, as “the multi-modal individualized Ayurveda treatment" was carried out in Germany, western standards of care were taken into account. "Cultural, infrastructural and legal" facets were also considered. For the sake of ensuring “comparable individualized conventional treatments”, an “evidence-based consensus” method was used to implement the resulting guideline-based conventional intervention. In addition, with the goal of ensuring treatment quality in both treatment groups, further specialists were employed. [Kessler 2018]

The “risk of serious side effects” stemming from either type of treatment for OA of the knee used in the trial can be considered low [Kessler 2018]. While four participants did experience one serious adverse event each (“fracture of radius, cholecystectomy, major depression episode, erysipelas; Ayurveda n = 3, conventional n = 1”), none of these events were identified as intervention related. Furthermore, no patients experiencing adverse events identified as intervention related developed "clinically relevant disease" or necessitated a hospital visit [Kessler 2018].

5.4.2 Limitations

The following section describes limitations related to the present study.

Recruitment Process

Based on the participant recruitment strategy in the present study, it is not likely that the enrolled participants reflect a representative sample of the general German population (**chapter 3.2**). While this might call into question the external validity of the study, such limitations can be put into perspective and/or countermeasures were taken.

Study participants were recruited through local newspaper advertisements as well as through acquisition in the regular outpatient clinics of the study centers. This is common practice when recruiting for clinical trials. Consequently, one could assume that the study participants were predominantly interested in receiving Ayurvedic treatment. However, all participants were extensively informed about the nature of the study in the screening process, including that the allocation to the treatment groups would be carried out only by chance via randomization. It should be noted that adherence was high in both groups and drop-out rates low and comparable in both groups.

Furthermore, due to the nature of the study interventions, it was not possible to carry out this study under double blind conditions. This is not a weakness of the study design but poses an inherent limitation of studies on such interventions where, by nature, blinding of the interventions is not possible. The double blind RCT was primarily developed for pharmacological trials and not for multimodality traditional medicine interventions. Therefore, it is difficult to rule out a bias in the results due to the expectations of patients and physicians. As a countermeasure, data reflecting the expectations of the participating patients and physicians were collected at the beginning of

the study (**Table 4.3**). A sensitivity analysis based on an ANCOVA-model was performed, which showed little effect of expectations on the overall outcome [Kessler 2018] (**chapter 4.3**).

While the recruitment criteria targeted participants aged 40-70 years, only participants between the ages of 55 and 64 were factually included in the study (**chapter 4.2**). This age group roughly corresponds to the target group that is usual in clinical OA knee care, see [Oliveria 1995], and thus represents the population suffering from knee OA.

A further limitation raised by Kessler et al. [Kessler 2018] refers to the "exclusion of individuals with obesity ≥ WHO grade II". However, less than 5 potential participants associated with obesity were excluded from participation in the study. Furthermore, the risk of developing OA of the knee rises to 60 % in subjects with body mass index (BMI) of 30 or higher [Murphy 2008], so that it could be argued that the excluded patients could first and foremost have benefitted from both interventions by weight loss would they have been included.

Even if women over 50 are more frequently and more intensely affected by knee OA than men [Kotlaz 2009], the study participant selection process did not reflect the exact gender representation of the German population with knee OA. In the present study, approximately three times as many women as men participated [Kessler 2018]. However, the gender distribution in both study groups was comparable.

Role of the Funding Source

As mentioned in chapter 3.9, the study was funded by a grant from the Ministry of AYUSH (formerly Department of AYUSH) through the Central Council for Research in Ayurvedic Sciences (CCRAS) under the AYUSH ministry. AYUSH/CCRAS are co-initiators in this context, which could be seen as a potential bias. However, the German research institution, all its involved research partners and the study team worked completely independently of the funding institution in developing the study design, conducting the study and analyzing the results according to strict international scientific criteria. Notably, this study was not contract research. Aim of this independent research project was to make a clinical comparison of OA treatment methods by a renowned European German research institution.

Use of Medication

Kessler et al. [Kessler 2018] stated that all patients, including Ayurveda patients, were permitted to use "conventional rescue medication" in addition to Ayurveda treatment. While this might be seen as a minor limitation, it was a requirement of the responsible university ethics committee, which was implemented compulsorily, but ultimately, had little effect on the results. Only 19% of the Ayurveda group compared to 81% of the conventional group made use of rescue medication during the 12-week intervention period.

The choice of medication in the conventional arm was also driven by external factors. Since in Germany patients often reject taking intra-articular corticosteroids, such treatments were not taken into consideration for this study [Kessler 2018]. Using intra-articular steroidal treatments as a part of conventional therapy could possibly have led to different results.

Furthermore, legal and ethical restrictions for herbal medical options in Germany prevented the full exploitation of traditional Ayurveda herbal therapies. The same applies to the use of leeches, which were also excluded from the Ayurveda arm for the same reason but are frequently part of traditional Ayurvedic therapy for OA knee. Perhaps even more substantial results in favor of Ayurveda could have been observed if all options of traditional Ayurvedic OA treatment had been integrated [Kessler 2018].

Time Limitations

The duration of the treatment sessions was different in both groups, with Ayurveda treatment sessions lasting 60-90 minutes and conventional treatment lasting 45-50 minutes. These time parameters were based on existing treatment standards in both treatment groups. Any change to these settings, either Ayurveda or conventional, would have led to inaccurate procedures not reflecting the respective system's standard approach for knee OA treatment [Kessler 2018].

Further Investigations

The study follow-up plan was structured to end after 12 months for the primary outcome and all other outcomes. In order to see sustainability effects, a longtime evaluation exceeding the 12 months study period would have been interesting. Unfortunately, this could not be implemented due to financial restrictions.

5.5 Comparison of Results with Other Studies

Chapter 2.2.2 provides an overview of a selection of publications of the last 20 years focusing on Complementary and Integrative Medicine in the treatment of knee OA. Only in a few cases does it make sense to make direct comparisons with the results of this study, as other studies differ fundamentally from the present study in terms of study designs, interventions and outcome parameters. The following chapter shows similarities and differences related to study designs and Integrative Medicine interventions. The aim of this chapter is to shed some light on the size and duration of effects of Ayurvedic treatment as analyzed here in comparison to other IM approaches.

As mentioned in **chapter 2.2.2**, Vas et al. used acupuncture as a complementary therapy to the pharmacological treatment of knee OA [Vas 2004]. In total, 97 patients were randomly separated into two groups, one group receiving acupuncture plus diclofenac and the other group receiving placebo acupuncture plus diclofenac over 12 weeks of treatment. Results suggest that acupuncture plus diclofenac is more effective than placebo acupuncture plus diclofenac for the symptomatic treatment of knee OA [Vas 2004]. Primary outcome measure was the WOMAC Index composed by its subscales (pain, stiffness and function). The results showed that a greater reduction was achieved in the intervention group in comparison to the control group (Mean Difference (MD) = 23.9 [15.0; 32.8], 95% Confidence Interval (CI)). The largest improvements were achieved on the WOMAC subscale function. The between-group difference was MD = 17.5 [11.0; 24.0]. For all WOMAC subscales the between-group differences were significant ($p < 0.001$). In comparison to the present study, both studies show a similar trend in pain reduction and physical function. Vas et al. used another validated WOMAC Index version ranging from 0 to 96 points. The effect size was not given in the publication by Vas et al., so the clinical relevance of the improvements cannot be compared directly with the present study.

Another study presented by Karner et al. investigated the effects of acupuncture in a double-blind RCT in OA of the knee [Karner 2013]. Blinded outcome assessment comprised knee flexibility and changes in pain measured by the WOMAC subscale pain. Over 116 patients with knee OA received three different treatments in a random order every seven days: classical acupuncture, modern acupuncture and non-specific need-ling as part of the control. Measurements were taken at baseline, immediately after

treatment, 3 days and 7 days after treatment. Results showed that the improvement in knee flexibility was significantly higher after classical Chinese acupuncture (SMD = 10.3 degrees [95% CI: 8.9, 11.7]) as compared to modern acupuncture (SMD = 4.7 degrees [95% CI: 3.6, 5.8]) [Karner 2013]. All methods achieved pain relief, with patient response rates of 48 % for nonspecific needling, 64 % for modern acupuncture, and 73 % for classical acupuncture [Karner 2013]. Since the parameter measurements were limited to the days immediately after treatment, comparisons of long-term effects to results of conventional treatments or complex multimodal Ayurvedic treatments over several weeks are limited. Comparing the results of Karner et al. with the present study, there are hints that the positive treatment effects in the Ayurveda group might be larger and more lasting. Acupuncture improved the WOMAC subscale pain from 16.3 to 10.5 immediately after treatment and worsens slightly to 12.8 within 7 days. Unfortunately, there are no follow-ups over a longer period of time. In the present study, the WOMAC subscale pain improves from 19.0 to 6.2 points in the intervention group within 12 weeks of treatment. Even 9 months after the last treatment, the value is still at 7.9. The improvements in the conventional group also persisted. However, the last measured value of 14.0 is on a similar level to that of acupuncture.

According to Michalsen et al. leeches therapy was a mainstay in conventional treatment of pain and inflammatory diseases throughout antiquity until the 20th century. Nowadays, its use is widespread in traditional healing procedures in Asia, Africa, and Arabic countries. Furthermore, there is renewed interest in leech therapy in the field of CIM and empirical evidence for specific benefit in knee OA [Michalsen 2007].

Lauche et al. performed a systematic review and meta-analysis of the effectiveness of medical leech therapy for patients with knee OA [Lauche 2014]. A total of 62 independent studies were screened. Only three RCTs and one controlled clinical trial (CCT), which compared leech therapy to other control conditions, were included, in which a total of 237 patients with OA of the knee participated. Leech therapy was administered only once or twice, and the focus was pain relief immediately after leech therapy. In terms of the selection of measurement, the authors' approach and that of this present study are comparable. Both used the WOMAC Index as the main outcome parameter, the subscales pain, function and stiffness and the SF-36 to measure quality of life. In order to ensure data comparability for the meta-analysis, for each outcome

Standardized Mean Differences (SMD) and 95 % confidence intervals had to be calculated. The authors note that it was necessary to standardize the results to a uniform scale before they could be combined [Lauche 2014]. A direct comparison with the present study is difficult, since in the meta-analysis a SMD mean value was calculated using four studies with four fundamentally different control groups. The control groups were integrative treatment program (health education, exercise, physiotherapy), topical diclofenac application twice daily, “sham” leeching and transcutaneous, electrical nerve stimulation. However, the overall results of the meta-analysis showed that there was strong evidence of immediate (SMD = −1.05; $p < 0.01$) and short-term pain reduction (SMD = −1.00; $p < 0.01$), immediate improvement in patients’ physical function (SMD = −0.72; $p < 0.01$) and immediate improvement in joint stiffness (SMD = −0.88; $p = 0.04$) [Lauche 2014]. Lauche et al. used the Cohen’s d-algorithm to determine the effect sizes. The results of the present study show after 12 weeks of treatment a medium effect size (SMD = 0.63), having a significantly stronger evidence ($p <0.001$) for all WOMAC subscales. Furthermore, the outcomes change only slightly over the follow-up-period of 12 months, while the long-term analysis in the meta-analysis shows a comparably small effect size (SMD = 0.2 to 0.5).

In the year 2016, Lauche et al. published a RCT investigating the effects of cabbage leaf wraps (CLWs) in the treatment of knee OA [Lauche 2016]. Patients received either treatment daily for 4 weeks with CLWs or a topical pain gel (TPG) with 10 mg diclofenac once a day or usual care (UC). Secondary outcomes included functional disability according to global WOMAC Index, WOMAC subscales (pain, stiffness, function) and quality of life (SF-36). In addition, the study examined self-efficacy according to Arthritis Self-Efficacy Scale-D, physical function by using the 30 s Chair Stand Test and Pressure Pain Sensitivity (PPS). The treatment took place for 4 weeks and a follow-up took place after 12 weeks. After 4 weeks, patients in the CLW group reported significantly less pain, higher quality of life and better physical function compared with the outcomes of the UC group. However, in comparison with the TPG group the between-group difference was not significant. Furthermore, no difference in pain intensity between CLW and UC or between CLW and TPG could be observed at 12 weeks. Significant differences between the CLW and UC groups could be observed for all WOMAC scales after 4 and 12 weeks [Lauche 2016]. In summary, CLWs were more effective in the treatment of knee OA than UC, but not better than TPG. Lauche et al. used an 11-point numerical rating scale for the

WOMAC subscales. Transferring the results of Lauche et al. to the German validated scale of the WOMAC Index, the outcome becomes quite comparable to the present study. Baseline measures and endpoint measures are of the same order of magnitude. A direct comparison between week 0 and week 12 shows that all results in the subscales pain (p), stiffness (s) and function (f) improved [*improvements in percent*]: CLW treatment [*p = 9.1 %, s = 9.1 %, f = 6.4 %*], Ayurveda treatment [*p = 25.6 %, s = 31.0 %, f = 24.8 %*], conventional treatment [*p = 13.2 %, s = 17.0 %, f = 12.9 %*]. Hence, in comparison to the present study, similar effects in pain reduction, physical function and improved quality of life were found, with improvements in the Ayurveda group being more pronounced.

Wang et al. showed that Tai Chi (2 times per week for 12 weeks) had beneficial effects similar to those of standard physical therapy (2 times per week for 6 weeks, followed by 6 weeks of monitored home exercise) in the treatment of knee OA [Wang C 2016]. The primary outcome was WOMAC Index score pain at 12 weeks. Secondary outcomes included physical function, depression, medication use, and quality of life. The WOMAC subscores pain and function were converted to scales of 0 to 100 [Wang C 2016]. In contrast to the present study, standard physical therapy was not a complex multimodal intervention, but followed the United States guidelines for knee OA treatment and consisted of two 30-minute outpatient sessions per week for 6 weeks. The study of Wang et al. showed that both groups had similar improvements in most secondary outcomes at 12 weeks and in all outcomes at 24 and 52 weeks. „The Tai Chi group showed greater improvement than the physical therapy group for most outcomes, but these differences were not statistically significant“ [Wang C 2016]. The results cannot be directly compared with the present study as the scaling conversion of the WOMAC Index applied by Wang et al. prevents a comparison using the absolute sizes of baseline data and outcomes at 12 weeks. However, in the present study, Ayurveda for knee OA showed significantly better results than the conventional treatment. The between-group differences were considerably better ($p < 0.001$) with clinically relevant effect sizes, e. g. WOMAC subscale pain with Cohen’s d 0.64 [95 % CI:0.32;0.97]. However, the effects on quality of life measured by the SF-36 are similar in both studies.

Bannuru et al. performed a meta-analysis with a focus on the efficacy of Curcumin and Boswellia for knee OA [Bannuru 2018]. A total of eleven RCTs were reviewed systematically. In order to achieve comparability of the different study results, Standardized Mean Differences (SMD) or Risk Ratios (RR) were calculated for all relevant outcomes. All studies showed that Curcuminoid- and also Boswellia-formulations were significantly more effective than placebo for pain relief and functional improvement. A comparison of Curcuminoid vs. Placebo revealed a statistically significant beneficial effect on pain, measured by VAS scales, in favor of Curcuminoid (SMD = −0.81 [95% CI: −1.25, −0.37]). In addition, a pooled analysis of two studies using the WOMAC subscale pain demonstrated an evidently smaller effect in favor of Curcuminoid (SMD = −0.47 [95% CI: −0.78, −0.16]). The direct comparison with the present study shows that the effect sizes according to WOMAC subscale pain are considerably better (SMD = 0.64 [95 % CI: 0.32; 0.97].) with Ayurveda for knee OA. Bannuru et al. conclude that herbal formulations could be a valuable addition to the treatment of knee OA. According to the authors' conclusion, the current evidence is insufficient to make meaningful recommendations for clinical practice, since large methodologically high-quality studies have not yet been conducted [Bannuru 2018].

Wang et al. published a meta-analysis where yoga was investigated as a treatment method for knee OA and rheumatoid arthritis [Wang Y 2018]. With the focus on the WOMAC Index as the primary outcome, 5 studies with 428 participants were identified. Based on the SMD using the global WOMAC Index, the authors came to the conclusion that yoga training leads to an improved knee function and is superior to the control group in terms of pain reduction. The authors state that "the SMD of WOMAC was −1.83 (95% CI −2.09, −1.57, $p < 0.05$, p for heterogeneity <0.05, $I^2 = 70.7\%$) that favored the yoga group. The pooled analysis indicated that yoga training was superior to the control group in restoring knee functions" [Wang Y 2018]. Since yoga has also been part of the present study, this meta-analysis is particularly interesting. After reviewing the individual studies, the effects in pain reduction and improvement of physical function of the yoga interventions were not quite as pronounced as in our complex multimodal Ayurveda intervention. The comparison with the absolute values of the present study shows that with Ayurveda treatment within 12 weeks an improvement from 91.1 to 30.0 points on the global WOMAC Index, from 19.0 to 6.2 points on the subscale pain, from 9.8 to 3.6 points on the subscale stiffness and from 62.3 to 20.2 points on the subscale function were achieved.

Perlmann et al. presented a study in which patients with knee OA were treated either with a whole-body Swedish massage or with light-touch or the so called “usual care”, corresponding to a standard treatment [Perlmann 2019]. The usual care treatment ended after 24 weeks. For groups, massage and light-touch, treatment ended after 8 weeks. Participants were assigned to continue with massage or biweekly light-touch or usual care for the remainder of the study until week 52. The primary outcome was the between-group difference on the WOMAC Index. The results after 8 weeks of treatment show, that massage in comparison to light-touch achieved significant improvements (SMD = −8.16 [95% CI: −13.50, −2.81]). The comparison between massage and usual care shows similar results (SMD = − 9.55 [95% CI: −14.66, −4.45]). However, Perlmann et al. conclude, that after 52 weeks any group difference in the change on WOMAC Index from baseline to 52 weeks was not significant ($p > 0.707$), indicating no significant difference in change across groups [Perlmann 2019]. In summary, it can be concluded that the greatest improvements occurred during the first 8 weeks of treatment and the results deteriorated over time significantly. A comparison to the present study shows, that highest improvements were achieved with Ayurveda during 12 weeks of treatment with a clinically relevant effect size (Cohen’s d 0.68 [95 % CI: 0.35; 1.01]). Furthermore, the improvements in both groups, Ayurveda and conventional, had a persistent effect.

In 2020 Wang et al. published a widely acclaimed randomized, double-blind, placebo-controlled study with Curcuma longa with 70 patients with knee OA [Wang Z 2020]. The study focused on the effects on localized effusion or synovitis in patients’ knees. The outcomes were assessed over 12 weeks. The primary outcome measure was pain intensity according on a VAS (Visual Analogue Scale). Compared to the placebo group the outcome measure showed significant improvements ($p = 0.039$, week 12). The authors also revealed that there were no significant changes in the effusion-synovitis volume by using Curcuma longa, according to the assessed magnetic resonance images (MRI). Unfortunately, there is no information about how long the effect of the pain reduction lasted beyond the study period.

A group of authors led by Singhal published a study in 2021 on turmeric compared to paracetamol for the treatment of patients with knee OA [Singhal 2021]. Turmeric is mainly used as a spice in Indian cuisine and as an Ayurvedic herbal treatment.

Curcumin is a bioactive compound that makes up a small fraction of the turmeric plant. In a RCT patients were randomly assigned into two groups to receive either a bioavailable turmeric extract 500 mg capsule two times daily or a paracetamol 650 mg tablet three times daily for 6 weeks. The outcome measures were the global WOMAC Index and the related subscales pain, stiffness and function. A scale from 0 to 96 points was used for the global WOMAC Index. After 6 weeks of treatment with turmeric extract, the outcome for global WOMAC Index, pain, stiffness, and function showed significant improvements. Moreover, in all outcome parameters, the turmeric treatment was better than or equivalent to the treatment with paracetamol (p-value < 0.05). The study concludes that turmeric extract is as effective as paracetamol in reducing pain and other symptoms of knee osteoarthritis [Singhal 2021]. The comparison of the global WOMAC Index with the present study shows that, within 6 weeks, the outcome in the turmeric treatment group improved by 13.9% (from 56.3 to 43.0 points) and in the paracetamol treatment group by 12.8% (from 50.2 to 37.9 points). As expected, the results of physical treatment of knee OA are better: The present study shows an improvement on the global WOMAC Index of 17.3 % after 6 weeks, and even 25.5 % after 12 weeks of Ayurveda treatment.

In summary, the field of IM is so broad that a direct comparison of diverse disciplines (acupuncture, leech therapy, effects of CLWs, tai chi, yoga, massage) is quite difficult, since the SMD can only represent one specific aspect. It should be noted that direct comparisons are limited between studies due to heterogeneity of outcome parameters, measurement scales, intervention durations and study visits. In the studies with a focus on meta-analysis in particular, the poor quality of the studies available for selection was mentioned. In general, it is noticeable that treatment methods such as Tai Chi [Wang C 2016] and Yoga [Wang Y 2018], in which physical movement and personal initiative (monitored home exercise) were a main focus, performed better in the results for stiffness and function. However, Tai Chi in particular, the authors concluded that the difference to the control group was not statistically significant [Wang C 2016]. On the other hand, acupuncture [Karner 2013], leech therapy [Lauche 2014], curcumin and Boswellia [Bannuru 2018, Singhal 2021] showed a positive short-term effect in pain reduction. In the present study, both Ayurveda and the conventional group showed significant improvement with a lasting effect. Furthermore, the difference between the two groups was significant for all WOMAC scales. Ayurvedic intervention showed more pronounced effects compared to other Integrative Medicine interventions, which is probably due to the complex multimodal intervention.

5.6 Triple Aim Framework

The treatment method evaluated in this study – Ayurveda – is “new territory”, at least when considered from the perspective of Western conventional standards. Inasmuch as the use of a “new” procedure, in this case Ayurveda for knee OA treatment, is aspired for a broader population outside its countries of origin, it is worthwhile to assess the opportunities and risks for a given society.

Berwick et al. presented how to improve the health care system with the help of “The Triple Aim” namely improving Health of Population, Enhancing Experience of Care, and Reducing per Capita Costs of Health Care [Berwick 2008]. It could be considered for future processes in the field of Traditional Indian Medicine, for example in the following way related to this study (see below):

Health of Population: Ayurveda follows (in general and also in the context of this study) a primarily salutogenetic approach. Health promotion and restoration of or re-approximation to health is at the centre of Ayurvedic thinking [Gupta 2009]. It is therefore in principle well compatible with conventionally defined levels of primary to quaternary prevention. In this study specifically, Ayurveda treatment is combined with lifestyle advice, knee-specific yoga posture advice, and daily self-applied knee massage (**chapter 3.7.1**). This support of the patient to act self-responsibly, leading to the active involvement in the treatment, could lead to a general improvement of public health if widely implemented.

Experience of Care: As demonstrated in this study, complex Ayurveda treatment leads to a higher reduction in knee complaints compared to conventional treatment and to an improvement of quality of life (**chapter 4.3**).

Costs per Capita: The study did not aim to examine economic criteria. Nevertheless, the general improvement in personal well-being observed in the study could lead to an extension of active participation in professional life. Slowing down the course of OA can lead to significant reduction of surgery, rehabilitation-costs, and pain medication and thus to a reduction of costs per capita. Ayurveda could possibly make a relevant contribution here.

Bodenheimer et al. [Bodenheimer 2014] expand Berwick's approach to include the “health care providers” dimension. This approach takes into account that increasing pressure on time and stress among healthcare professionals lead to negative frustration. The consideration of the additional dimension is based on the fact that a positive engagement of the staff is decisive in order to pursue the main goals of the Triple Aim Framework.

Health Care Providers: The presented study suggests that traditional therapies such as Ayurveda may take comparatively more time than conventional care per patient (**chapter 3.7.2**). Such treatments are often specially tailored to the individual needs of the patients. An explicit study to examine the work satisfaction of „health care providers“ working with Ayurvedic therapies in Western contexts does not yet exist. However, it is reasonable to assume that individual treatments with a higher time contingent may also lead to less time pressure and less stress for the involved personnel. Systematic investigations on this subject would be desirable for the future.

5.7 Conclusion and Outlook

In this study the effectiveness of Ayurveda therapy in patients with knee OA was examined. For this purpose, a multicenter randomized controlled intervention study was carried out over 12 weeks with parallel group comparison and a follow-up after 6 and 12 months. An Ayurveda treatment group (intervention group) was compared with a conventional care group (control group). The multi-component Ayurveda intervention followed traditional treatment principles of Ayurveda and was adapted to the individual needs of the patients. Specialists in the field of orthopedics and orthopedic surgery performed guideline-based conventional conservative treatments for the study participants in the conventional group. In both groups, treatments for each participant were carried out in 15 sessions over an intervention period of 12 weeks. Additionally, mid- and long-term treatments effects were measured at 6- and 12-month follow-ups. The main outcome parameter was the change on the WOMAC Index after 12 weeks. In addition, the following validated questionnaires were used as secondary outcomes: WOMAC-subscales, Pain Disability Index (PDI), Pain Experience Scale (SES), Profile of Mood States (POMS), Short Form-36 Health Survey (SF-36) and Numeric Rating

Scales (NRS) for pain and sleep quality. Data on rescue medication, patient expectations, and safety were also recorded. In total, 151 patients were randomly assigned either to the Ayurveda group or to the conventional group. A reduction of knee OA complaints could be observed for both treatment groups. Notably, the improvements in the Ayurveda group were significantly higher related to the primary outcome when compared to the control group findings and to a large fraction of the secondary outcomes as well. Additionally, even at 6- and 12-month follow-ups WOMAC Index data indicate that the improvements are sustainable in both groups, but significantly in favor of the Ayurveda group.

Though the Ayurvedic treatment in this study resulted in significant improvement of knee OA complaints, the following aspects could be incorporated into future studies in the field, covering various facets of Ayurvedic treatment under Western circumstances:

A key feature and strength of the present study was the implementation of multimodality treatment. This set it apart from all previous studies of Ayurveda treatment of OA in which single aspects were focused on, such as herbal / botanical treatments [Kessler 2015]. However, since the treatments were individualized in this multimodality approach, it is difficult to impossible to decipher which component contributes how and to what extend to the overall effect. Additional refined Whole Systems Research and Mixed-Methods approaches would be desirable here for future projects in the field.

Furthermore, patient WOMAC Index values were assessed for a period of 12 months. In order to see effects of a long-time evaluation, which is of socio-economic interest in the field of OA, it would be worthwhile to include even longer follow-up periods in future studies, such as 24- and 36-month follow-ups.

In order to avoid any criticism of potential biases by institutions linked to the promotion of Ayurveda (such as the Indian AYUSH Ministry), optimized public research funding options in the field of Integrative Medicine would be very desirable within Germany and the EU. For example, research calls from the Federal Ministry of Education and Research (BMBF) or the German Research Society (DFG) could be very helpful to further improve, quality and impact of clinical research on Ayurveda and related disciplines. To date, such options do not exist yet or only to a limited extend.

It was pointed out in the limitations section (**chapter 5.4.2**) that the use of intra-articular corticosteroids in the conventional group and the full range of Ayurvedic herbal treatment options and leeches had to be excluded from this study due to legal and ethical restrictions. Such treatment aspects could be included in future research and should also be considered in subsequent studies and settings outside of Germany where different regulations apply.

As mentioned in **chapter 5.6**, the study did not aim to examine economic criteria. Thus, questions regarding economic aspects of individualized multimodal Ayurveda treatments remain open and largely unanswered. In future research, transdisciplinary and interprofessional approaches including cost-effectiveness analyses should be integrated in order to evaluate whether such approaches fulfill the Triple Aim aspect of Costs per Capita.

The results of this study suggest that Ayurveda – as used here – is effective in the treatment of OA of the knee. In any case, the data suggest that Ayurveda could be used as a complementary therapy, in addition to conventional treatment, that Ayurveda OA care can be implemented in Western settings, and that the therapeutic effects seem to be sustainable. This study could serve as a source of inspiration and starting point for further research in this field.

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7. Eidesstattliche Versicherung

„Ich, Michaela Spoo, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema „Comparative Effectiveness of Ayurveda treatment and conventional Care in Knee Osteoarthritis – a Randomized Controlled Trial“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE -www.icmje.org) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s. o.) und werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

8. Anteilserklärung

Kessler CS, Dhiman KS, Kumar A, Ostermann T, Gupta S, Morandi A, Mittwede M, Stapelfeldt E, Spoo M, Icke K, Michalsen A, Witt CM (2018). Effectiveness of an Ayurveda Treatment Approach in Knee Osteoarthritis – A randomized controlled Trial. Osteoarthritis and Cartilage, Volume 26, Issue 5, May 2018, Pages 620-630. https://doi.org/10.1016/j.joca.2018.01.022.

Ich hatte folgenden Anteil an dieser Publikation:

Im Rahmen der CARAKA-Studie war ich an der gesamten Dateneingabe, am Data-Cleaning sowie der Datenauswertung hauptbeteiligt. Des Weiteren war ich mitbeteiligt an der Datenakquise. Für die Mitarbeit an der Publikation bedeutet dies konkret eine Mitarbeit am Schreiben des Manuskripts, am Methodikteil, an den Tabellen und Graphiken im Ergebnisteil sowie an der Diskussion.

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers

Unterschrift der Doktorandin

9. Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

List of Publications

Kessler CS, Dhiman KS, Kumar A, Ostermann T, Gupta S, Morandi A, Mittwede M, Stapelfeldt E, Spoo M, Icke K, Michalsen A, Witt CM (2018). Effectiveness of an Ayurveda Treatment Approach in Knee Osteoarthritis – A randomized controlled Trial. Osteoarthritis and Cartilage, Volume 26, Issue 5, May 2018, Pages 620-630. https://doi.org/10.1016/j.joca.2018.01.022.

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