

https://dspace.org/

Exercise training and low level laser therapy as a modulate to pain relief and functional changes in knee osteoarthritis

Kholvadia, Aayesha

2019

https://hdl.handle.net/10539/29133

Kholvadia, Aayesha (2019) Exercise training and low level laser therapy as a modulate to pain relief and functional changes in knee osteoarthritis, University of the Witwatersrand, Johannesburg, <http://hdl.handle.net/10539/29133>

Downloaded from a DSpace repository. https://dspace.org/

EXERCISE TRAINING AND LOW LEVEL LASER THERAPY AS A MODULATE TO PAIN RELIEF AND FUNCTIONAL CHANGES IN KNEE OSTEOARTHRITIS

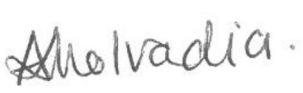
Aayesha Kholvadia

A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Doctor of Philosophy

Johannesburg, 2019

DECLARATION

I, Aayesha Kholvadia, declare that this thesis is my own, unaided work. It is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University. The required convention for referencing the work of others has been followed.



_____

Aayesha Kholvadia

Date: 28 July 2019

STUDENT'S CONTRIBUTION TO THE WORK PRESENTED IN THE THESIS

- Together with my supervisors, I was involved in the conceptualization of data collection, synthesis and reporting of thesis together with the publications arising from the thesis.
- I developed and validated the questionnaire (Deemed KOA management paradigm).
- I collected data for all three data collection sections of the thesis, and contributed to (with the help of my supervisors) to quality control and data management of the survey.
- I collected, stored and analysed the data for statistical analysis.
- My specific responsibilities for the submitted publications are outlined in the text and all the co-authors of these manuscripts have approved the inclusion of these in the thesis. [Appendix 10]

PUBLICATIONS AND PRESENTATIONS IN SUPPORT OF THIS THESIS

Publications

Kholvadia, A., Gradidge, P.J.L. and Constantinou, D. The efficacy of low level laser therapy and exercise for knee osteoarthritis. Submitted to the South African Journal of Sport Medicine.

Contributions to the paper

Aayesha Kholvadia conducted the study, performed the statistical analysis, and wrote the paper. All authors read, commented and approved the final version of the manuscript.

Oral Research Presentations

Kholvadia, A., Gradidge, P.J.L. and Constantinou, D. (2017). Use of Low Level Laser Therapy in the Management of Knee Osteoarthritis (Oral presentation). *South African Laser Committee Congress, Stellenbosch, September 2017*.

Kholvadia, A., Gradidge P.J.L. and Constantinou, D. Exploring the efficacy of low level laser therapy and exercise for knee osteoarthritis (Lecture presentation). *Centre for Exercise Science and Sports Medicine, University of the Witwatersrand, June 2018*.

Kholvadia, A., Gradidge, P.J.L. and Constantinou, D. Exploring the efficacy of low level laser therapy and exercise for knee osteoarthritis (Oral presentation). *Faculty of Health Sciences Research Day, University of the Witwatersrand, 6 September 2018*.

Kholvadia, A., Gradidge, P.J.L. and Constantinou, D. Exploring the efficacy of low level laser therapy and exercise for knee osteoarthritis (Invited speaker). *Meditech laser symposium, Vancouver – Canada, 30 September 2018*.

GRANTS

Title of grant: National Research Foundation (NRF) Masters and Doctoral scholarship

Principal investigator: Ms Aayesha Kholvadia

Total amount allocated: R200 000.00

The money was used for:

Contributing towards data collection and thesis synthesis (R50 000.00), presentation at International Laser Symposium (R80 000.00), calibration of laser equipment (R20 000.00), research assistance (R5 000.00) and language editing (R5 000.00).

Title of grant: Postgraduate PhD Merit award

Principal investigator: Ms Aayesha Kholvadia

Total amount allocated: R24050.00 and stipend of R2 500.00

The money was used for: The payment of tuition fees in 2017

ACKNOWLEDGEMENTS

I would like to acknowledge and thank the following people for their contributions towards completion of this thesis:

- The Almighty Allah for providing me with this opportunity to contribute to the body of knowledge and making a difference in the lives of people.
- My dearest husband, for his emotional, physical, financial and spiritual support. You are a man-in-a-million and as proud of me as you are, I am just as proud of you.
- My parents and siblings; for their support. Thank you so much! You have supported and pushed me when I didn't see an end - thank you.
- My supervisors, Professor Demitri Constantinou and Doctor Philippe Gradidge for your patience, guidance, support and motivation (and tissues for the many tears) during my study. Thanks a Million!
- The National Research Foundation of South Africa (NRF) and University of the Witwatersrand Post-Graduate Financial Aid for the financial backing of the study. Opinions expressed, and conclusions arrived at, are those of the author and are not necessarily to be attributed to the NRF.
- All the study participants without whom this study would not have been possible. Your enthusiasm, time and dedication is much appreciated. Many of you have humbled me and taught me many life lessons – thank you!
- To my friends and colleagues, all of whom have provided me with emotional and motivational support, not forgetting the all-important statistical support, I appreciate the time and effort that had been dedicated to me. You guys are the best!

- A very special thank you to the participants that consented to this research project, thank you for allowing me into your lives. I hope that you learned as much from our interactions as I did. May God bless you, protect you and allow you to lead a long productive life.

DISCLAIMER

Any opinion, findings and conclusions or recommendations expressed in this material are those of the author(s) and therefore the NRF does not accept liability in regard thereto.

LIST OF ABBREVIATIONS

- ADL – Activities of daily living
- ANOVA – Analysis of variance
- AP – Allied Practitioner
- cm – centimetre
- DP – Distal patella
- GP – General Practitioner
- J – joules
- KOA – Knee Osteoarthritis
- LED – Light Emitting Diode
- LLLT- Low level laser therapy
- Max - Maximum
- Min - Minimum
- mm – millimetres
- MP- Mid patella
- mW – milliwatts
- NCDs – Non-communicable diseases
- nm – nanometer
- NSAIDs – Non-Steroidal Anti-inflammatory Drug
- OA – Osteoarthritis
- PP - Proximal patella
- ROM – Range of motion
- RCT – Randomised Controlled Trial
- SAIDs – Steroidal Anti-inflammatory Drugs
- SD- Standard deviation

- SP- Specialist practitioner
- TKR – Total knee replacement
- W – watts
- WHO – World Health Organization
- WOMAC - Western Ontario and McMaster Universities Osteoarthritis index

ABSTRACT

Background Evidence shows that the global prevalence of knee osteoarthritis (KOA) is high, with limited data on the management of the disease. The use of novel modalities to treat the condition is low due to poor understanding of their clinical effects. Therefore there are gaps in the knowledge on the prevalence and treatment modalities for patients diagnosed with KOA.

Aim: The aim was threefold; (i) to determine the prevalence of KOA in South Africa aged 45yrs-75yrs; (ii) to determine the current management of KOA; and (iii) to determine the effect of Low Level Laser therapy (LLLT) on the structural and functional components related to KOA in a South African cohort, aged 45-75yrs.

Methods: The methodology will be discussed in terms of the three specified objectives; (i) prevalence study data - a self-reported data collection sheet listing 19 relevant ICD 10 codes; completed by South African medical aid providers. (ii) The treatment paradigm study, which encompassed a deemed KOA management paradigm validated questionnaire sent electronically to 742 general, specialist and allied practitioners, identifying the incidence of KOA and deemed efficacy and compliance of various management tool. These practitioners were identified from a database of medical and allied practitioners in both the private and public sector of South Africa. The questionnaire consisted of two close ended questions indicating the incidence of KOA and bilateral KOA patients consulted at the practice; one choice question indicating the most suggested mode of therapy from a choice of pharmaceutical, surgical, homeopathic, physical exercise therapy and LLLT and

finally, 3 Likert type scale questions on the deemed efficacy and compliance of the modes of therapy as stated above. (iii) The intervention study which was a randomized controlled trial (RCT) utilizing pre marked questionnaire sheets on 111 participants. Participants were randomized into one of three intervention groups; (1) exercise group (n=39), (2) LLLT group (n=40), and (3) combined exercise-LLLT group (n=32). Data on knee circumference, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), knee range of motion (ROM) and the one minute timed sit–to-stand test was used. These tests were done at four time points: (T1) baseline, (T2) post-12 session intervention, (T3) one month post intervention and (T4) three months post intervention.

Results: The results will be discussed in terms of the three specified objectives; (i) The prevalence of KOA was reported as 17.5%, 28.0% and 38.5% in a South African population over 45yrs. (ii) Four hundred and thirteen clinicians completed the questionnaire, reporting a KOA patient intake of 53%. Pharmacology (36.3%) and physical exercise (35.3%) was the most common management protocols compared to surgical intervention, homeopathy and LLLT. Pharmacotherapy (73%) and physical exercise (92%) were observed as effective treatments. Seventy five percent of all practitioners responded with an answer of “no comment” when asked the deemed efficacy of LLLT. Practitioners viewed patients with KOA to have low compliance with physical exercise and pharmacotherapy (iii) the participant demographic included 86 females and 25 males, the average age reported was 61.8 $\pm$ 5.6yrs. At 12-week follow-up, knee circumference decreased significantly in all groups ($p<0.05$), the effect was highest in the LLLT group. All groups experienced improvements in the WOMAC pain scale, but the LLLT group showed the greatest improvement ($p<0.05$). Knee

ROM values improved significantly across all three groups; however, the effect of the intervention was most significant ($p<0.005$) in the combined LLLT-exercise group. Physical functionality scores showed a greater improvement in the combined LLLT-exercise group at all three data collection points.

Conclusions: The estimated prevalence of KOA is 17-35% based on data collected from a specified South African cohort. Pharmacotherapy is a commonly suggested KOA management mode, whilst clinicians view physical exercise as effective. LLLT was not a known tool for the treatment of KOA. In addition to the improved functionality observed, pain was lowered significantly, particularly in the combined exercise-LLLT group. Study results have shown that LLLT used in isolation or in combination with physical exercise is an effective management tool.

Keywords

Physical exercise, Low Level Laser therapy, Knee osteoarthritis

TABLE OF CONTENTS

Contents

DECLARATION 2
STUDENT'S CONTRIBUTION TO THE WORK PRESENTED IN THE THESIS 3
PUBLICATIONS AND PRESENTATIONS IN SUPPORT OF THIS THESIS 4
Publications 4
Oral Research Presentations 4
GRANTS 5
ACKNOWLEDGEMENTS 6
DISCLAIMER 8
LIST OF ABBREVIATIONS 9
ABSTRACT 11
TABLE OF CONTENTS 14
LIST OF FIGURES 18
LIST OF TABLES 19
DEFINITION OF TERMS 20
STRUCTURE OF THE DOCUMENT 22
CHAPTER 1: 23
1. STUDY BACKGROUND 23
1.1 Introduction 23
1.2 Problem Statement 25
1.3 Research Questions 25
1.4 Aim and Objectives of The Study 26
1.4.1 Aim 26
1.4.2 Objectives 26
1.5 Significance of the study 26
PART 1 28
CHAPTER 2 29
2. LITERATURE REVIEW 29
2.1 Introduction 29
2.2 History and Background on the Definition and diagnosis of KOA 29
2.3 Pathophysiology of KOA 32
2.4 Clinical Features of KOA 33
2.5 Aetiology of KOA 34

2.6 Epidemiology of Knee Osteoarthritis 34
2.7 Selected Management Modalities for Knee Osteoarthritis 37
2.7.1 Non-invasive therapies 42
2.7.2 Pharmacotherapy 45
2.7.3 Surgical intervention 47
2.7.3. Regenerative medicine 50
2.8 Exercise as a Management Tool for Knee Osteoarthritis 51
2.9 Low Level Laser Therapy 53
2.9.1 Mechanism of low level laser therapy 54
2.9.2 Laser parameters 56
2.9.3 Evidence for the effectiveness of LLLT in musculoskeletal conditions 57
2.9.4 Exercise and LLLT as co-modalities for the treatment of KOA 59
2.10 Summary 60
2.11 Research Gaps 61
3. METHODOLOGY 62
3.1 Introduction 62
3.2 Prevalence Study 62
3.2.1 Study design 62
3.2.2 Sampling technique and randomisation 62
3.2.3 Sample size 63
3.2.4 Data collection and analysis 63
3.3 Treatment Paradigm Study 63
3.3.1 Content validity of questionnaire 64
3.3.2 Study design 65
3.3.3 Sampling technique 66
3.3.4 Sample size 66
3.3.5 Data collection and analysis 67
3.4 Intervention Study 67
3.4.1 Study design 68
3.4.2 Sampling technique and randomisation 68
3.4.3 Sample size 69
3.4.4 Study site 70
3.4.5 Inclusion and exclusion criteria 70
3.4.6 Data collection 71
3.4.7 Data analysis 74
3.5 Intervention Programme 75

3.5.1 Low level laser therapy 75
3.5.2 Exercise intervention 76
3.6 Ethical Considerations 76
3.7 Summary 77
PART 2 78
CHAPTER 4 79
4. RESULTS 79
SECTION A 79
4.1 Prevalence Study 79
4.4 Treatment Paradigm Study 80
4.3.1 Practice delineation 80
4.3.2 Percent of total patients observed with diagnosed KOA 80
4.3.3 Treatment modes 81
4.3.4 Deemed treatment mode effectiveness 82
4.3.5 Deemed Compliance of proposed treatment modes 85
SECTION B 88
4.3 Intervention Study 88
4.3.1 Subject characteristics 88
4.3.2 Baseline characteristics 89
4.3.5 Baseline (T1) to1 month post intervention (T3) 92
4.3.5 Baseline (T1) to 3 months post 12 session intervention (T4) 93
4.4 Knee Osteoarthritis Variable Outcomes 93
4.4.1 Knee circumference 93
4.4.2 WOMAC pain scale 94
4.4.3 Knee ROM 95
4.4.4 Sit-to-stand 95
4.5 Intervention study discussion 96
4.5.1 Knee circumference 97
4.5.2 WOMAC pain scale 97
4.5.3 Knee range of motion (flexion and extension) 98
4.5.4 Physical functionality 99
CHAPTER 5 101
5. DISCUSSION 101
5.1 Introduction 101
5.2 Summary of the main thesis findings 101
5.3 Emerging Themes from the PhD 102

5.3.1 Difficulty estimating KOA prevalence 103
5.3.2 Knowledge on selected non-surgical management strategies for KOA 104
5.3.3 Novel approaches to the management of KOA 106
CHAPTER 6 108
6. LIMITATIONS, RECOMMENDATIONS AND CONCLUSIONS 108
6.1 Limitations 108
6.2 Theoretical Relevance and Implication of Findings 108
6.3 Recommendations 109
6.4 Conclusions 109
References: 111
APPENDIX 1: ETHICAL CLEARNACE CERTIFICATE 136
APPENDIX 2: LETTER TO MEDICAL SCHEMES REGARDING THE INCIDENCE OF KNEE OSTEOARTHIRITIS 137
APPENDIX 3: STUDY OUTLINE – MEDICAL PRACTITIONER 139
APPENDIX 4: DATA RECORDING / EVALUATION SHEET 144
APPENDIX 5: WESTERN ONTARIO AND MCMASTER UNIVERSITIES ARTHRITIS INDEX (WOMAC) SCORE 146
APPENDIX 6: LOW LEVEL LASER THERAPY OUTLINE 150
APPENDIX 7: EXERCISE THERAPY OUTLINE 152
APPENDIX 8: STUDY OUTLINE FOR THE PARTICIPANT 155
APPENDIX 9: INFORMATION SHEET AND INFORMED CONSENT FORM 159
APPENDIX 10 : CO-AUTHOR PERMISSION 163

LIST OF FIGURES

FIGURE 1: GRAPHICAL REPRESENTATION OF PHD THESIS 22

FIGURE 2: PATHOPHYSIOLOGY OF THE OSTEOARTHRITIC KNEE 33

FIGURE 3: OSTEOARTHRITIS MANAGEMENT PRINCIPLES 37

FIGURE 4: MECHANISM OF LOW LEVEL LASER THERAPY 55

FIGURE 5: INTERVENTION STUDY: SAMPLE SIZE ALTERATIONS 70

FIGURE 6: PREFERRED KOA MANAGEMENT TOOL AMONGST A SOUTH AFRICAN HEALTHCARE PRACTITIONER COHORT 82

FIGURE 7: COMPARABLE EFFECTS OF EXERCISE VS LLLT OR EXERCISE VS COMBINATION THERAPY ON VARIABLES OF KOA 96

LIST OF TABLES

TABLE 1: REVIEW OF THE DEFINITION AND DIAGNOSIS OF KOA (1986-2016)30

TABLE 2: SUMMARY OF SELECTED KOA MANAGEMENT MODES..... 38

TABLE 3: LASER PARAMETERS..... 56

TABLE 4: PILOT STUDY: QUESTIONNAIRE..... 64

TABLE 5: LOW LEVEL LASER THERAPY DOSAGE..... 75

TABLE 6: DESCRIPTIVE DATA: DEEMED KOA PREVALENCE..... 79

TABLE 7: KOA STATISTICS: DESCRIPTIVE DATA 81

TABLE 8: DEEMED EFFICACY OF FIVE KOA MANAGEMENT PROTOCOLS 83

TABLE 9: DEEMED COMPLIANCE OF FIVE KOA MANAGEMENT PROTOCOLS 85

TABLE 10: INTERVENTION STUDY: PARTICIPANT DEMOGRAPHIC..... 88

TABLE 11: BASELINE AND POST INTERVENTION CHARACTERISTICS OF THE SAMPLE..... 89

TABLE 12: KOA OUTCOMES (T2, T3, T4) – ADJUSTED MEAN CHANGES AND EFFECT SIZES BY INTERVENTION GROUP 91

DEFINITION OF TERMS

For the purposes of this PhD thesis.

- **Knee Osteoarthritis** – A chronic medical condition affecting the knee joint in which the cartilage at the bone surface wears down.
- **Low Level Laser Therapy** – A form of medical intervention applying a light source through Light Emitting Diodes (LED's) to the surface of the skin, used in the management of knee osteoarthritis.
- **Medical Aid Scheme** – A form of an insurance company providing funding for medically related procedures for its client.
- **Medical practitioner** – A practitioner registered with the Health Professionals Council of South Africa (HPCSA) able to treat a citizens by diagnosing a condition and dispensing various treatment modes in the management of a KOA diagnosis. For the purpose of this thesis medical practitioners were doctors also known as general practitioners in South Africa.
- **Natural Healing Practitioners** – For the purpose of this thesis were defined as practitioners utilizing natural sources such as plant sources to treat citizens.
- **Osteoarthritis** – For the purpose of this thesis osteoarthritis is defined as a synovial joint disorder experiencing a loss of articular cartilage, thickening of joint capsule and hypertrophy of the bone.
- **Pain** – there are varied definitions of pain. For the purpose of this research study the definition by (Hanoch Kumar and Elavarasi, 2016) "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, will be defined.

- **Physical exercise therapy** – The performance of physical activity to develop or maintain physical fitness and health. For the purpose of this thesis physical exercise refers specifically to an outlined set of physical movements prescribed for maintaining and / or improving functionality of the muscles associated with the knee joint.
- **Randomised Controlled Trial** – A research study in which participants are allocated randomly to a particular intervention protocol. The study has a protocol with a control measure for comparison and an intervention measure to test effectiveness.
- **Specialist Practitioner** – Are medical practitioners who have completed advanced training and or research in a particular field of medicine. For the purpose of this thesis specialist practitioners included orthopaedic surgeon, general surgeons and rheumatologists.

STRUCTURE OF THE DOCUMENT

The PhD thesis is with an article submitted for publication and there are three parts to it (Fig 1):

- Chapter 1 includes the study background, problem statement, the research question, the study aims and objectives together with the significance of the study.
- Part 1 comprises the literature review (Chapter 2) and the consolidated methodology (Chapter 3).
- Part 2 comprises the results and discussion (Chapters 4 and 5).
- Part 3 is the final component of the thesis and includes the conclusions and suggestions for future research (Chapter 6).

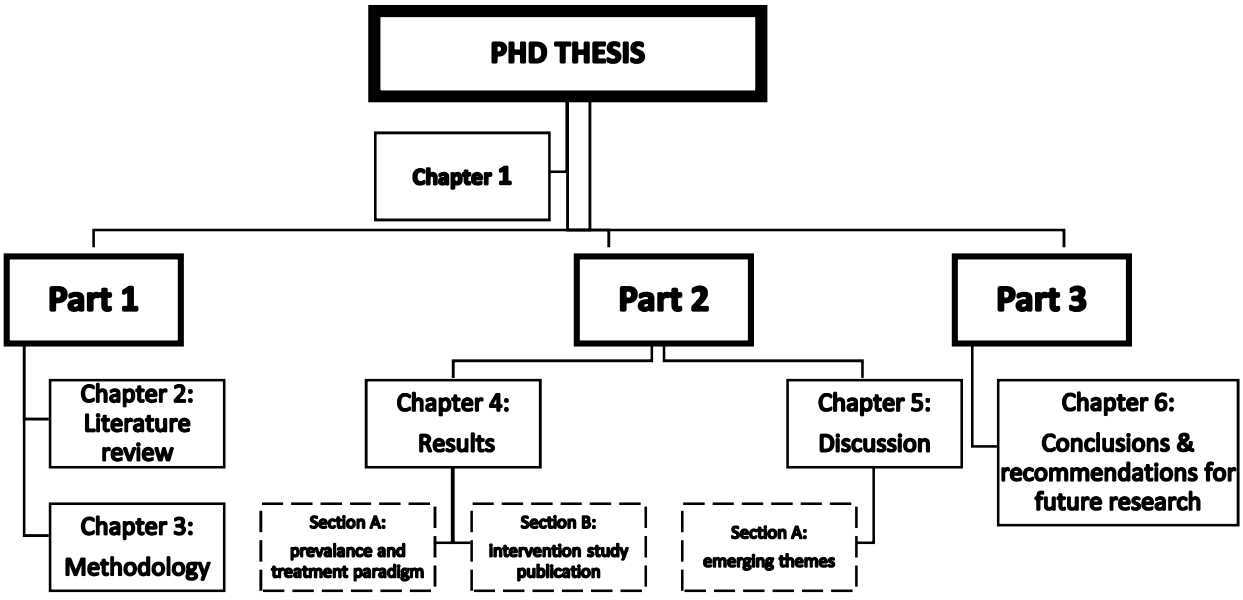


FIGURE 1: GRAPHICAL REPRESENTATION OF PHD THESIS

CHAPTER 1:

1. STUDY BACKGROUND

1.1 Introduction

Knee Osteoarthritis (KOA) is classified as a chronic disorder with functional, social and economic burdens (Arden, Blanco and Cooper, 2015). Literature on identifying, diagnosing and treating KOA, varies from subjective assessments to clinical radiographic imaging, while treatment modalities range from single facet pharmacological interventions to multifactorial treatment approaches (Arden and Nevitt, 2006). The symptoms and disease severities differ amongst diagnosed patients but are usually noticed in advanced stages and are therefore multifactorial. Similarities include pain and radio-graphical changes seen within the joint (Arden *et al.*, 2009).

In the literature on the epidemiology and prevalence of KOA, there seems to be a general agreement both nationally and internationally that KOA presents with pain and stiffness, resulting in significant disability and decreased functionality (Silverwood *et al.*, 2015; Usenbo *et al.*, 2015). KOA is reported to be the tenth leading cause of the global non-fatal burden of disease, a major source of disability in the elderly (Quintana *et al.*, 2006).

Knee osteoarthritis is multifactorial and of multiple aetiology; therefore, the goal of treatment is to alleviate the symptoms and slow the progression (Roos and Arden, 2015). The therapeutic spectrum ranges from conservative physical exercise to aggressive medical intervention and surgery in advanced disease progression (Joern *et al.*, 2010). Physical exercise therapy is widely recommended in South African and

international guidelines for managing KOA and includes land-based exercise and aqua-therapy (Palazzo *et al.*, 2016).

Studies in the field of therapeutic medicine have yielded some important insights into the use of low level laser therapy (LLLT) for the treatment of KOA (Alfredo *et al*., 2012, 2018; Alghadir *et al.,* 2014; Brosseau *et al*., 2000; Gur *et al*., 2003; Soleimanpour *et al*., 2014).

Low Level Laser therapy (LLLT) acts to improve reparative properties in cartilage (Brosseau *et al.,* 2000; Fukuda *et al*., 2011), aiding in the structural benefits of employing this treatment mode for the management of KOA. Studies by Bülow, Jensen and Danneskiold-Samsøe, (1994); Alfredo *et al.*, (2012) showed positive improvements in chronic pain levels in KOA patients undergoing LLLT in isolation or as a combined treatment modality. A randomized control trial (RCT) published by Alfredo *et al*., (2012) concluded that LLLT reduces pain and improves patient functionality compared to a placebo. In publications by Fukuda *et al.*, (2011); and Alfredo *et al*., (2012, 2018) the authors noted positive effects when using LLLT combined with exercise on variables such as range of motion (ROM), muscular strength and quality of life. The use of LLLT as a treatment modality is increasing, however data on its use in KOA management is limited, therefore the purpose of this PhD thesis was to document the incidence of KOA within South Africa, identify a management paradigm amongst South African practitioners on the treatment of KOA and document the effects of exercise and LLLT used in isolation or as a combined therapy on the structural and functional aspects of KOA.

1.2 Problem Statement

The evidence shows that the prevalence of KOA is high, particularly amongst an ageing population. Data on the management of this condition are limited, particularly in developing contexts such as South Africa. The use of novel modalities to treat KOA is low due to poor understanding of their clinical effects.

Currently, there are no published data on the incidence and optimal treatment of KOA within the sub-Saharan African context. There is therefore a gap in the knowledge on the prevalence and treatment modalities for patients with KOA.

In addition, the knowledge gained from this study will add value to the national and international body of knowledge by highlighting areas of combinative therapies such as physical exercise and LLLT for the treatment of KOA.

1.3 Research Questions

The appropriate research questions are:

(i) What is the current prevalence rate of KOA in South Africa amongst South African males and females aged 45-75yrs?

(ii) What is the current management paradigm of KOA amongst medical practitioners and allied professionals in South Africa?

(iii) What are the effects of using exercise and LLLT in isolation or as co-modalities on the structural and functional aspects of KOA on a South African cohort, aged 45yrs-75yrs?

1.4 Aim and Objectives of the Study

1.4.1 Aim

The aim of this PhD was to investigate the prevalence of KOA and management strategies for KOA; and to determine the efficacy of exercise and LLLT on KOA.

1.4.2 Objectives

The objectives of the PhD were to:

- To investigate the prevalence of KOA in South Africa amongst males and females aged 45-75yrs
- To underline the current management strategies in a cohort of patients diagnosed with KOA
- To establish the effects of exercise and LLLT on the functional components of KOA in a cohort diagnosed KOA patients from the southern areas of Johannesburg, South Africa

1.5 Significance of the study

In a systematic review by Usenbo *et al.*, (2015), the authors concluded that there is a lack of prevalence data on arthritis in sub-Saharan African countries, highlighting the need for updated data. The World Health Organization's (WHO) warns that non-

communicable diseases (NCD's) such as osteoarthritis (OA) will continue on an upward pattern of increase, thus placing a higher burden on early mortality due to NCDs. Osteoarthritis has a significant impact on disability, with reports showing a 45% increase from 1990 to 2010 (Cross *et al*., 2014). This PhD study will provide updated data on the prevalence of KOA amongst a determined sample of the South African population.

The goal of treatment for KOA is to alleviate symptoms and slow the progression (Joern *et* al., 2010; Ringdahl and Pandit, 2011). While the therapeutic spectrum is varied, authors Grol and Grimshaw, (2003), reported that practitioners are not always aware of adjunct therapies available to assist patients with KOA. Highlighting the current insights into the management of KOA, the study indicates management avenues requiring further exploration and contributes to the body of knowledge by ascertaining viewpoints and educating practitioners on using alternative therapy modes in the management of KOA.

Laser therapy has gained popularity within the field of therapeutic medicine since its initial used in the mid 1960's, however, its effectiveness in KOA rehabilitation is still controversial (Chung *et al.*, 2012). Consensus has not been reached due to variations in the equipment used, experimental design and techniques employed for data collection and reporting (Gur *et al*., 2003; Rayegani *et* al., 2017). This PhD study will determine the effects of exercise and LLLT as co-modalities for the management of KOA.

PART 1

CHAPTER 2

2. LITERATURE REVIEW

2.1 Introduction

Knee Osteoarthritis (KOA) is a dominant type of OA with the likelihood of developing KOA increasing with age (Joern *et* al., 2010; Cross *et al*., 2014; McAlindon *et al*., 2014). It is this dominance of the type of OA and its prevalence that warrants the need for clinical studies on the effective management of the disorder. Symptoms and severity differ between KOA patients due to varied stages and confounding comorbidities, while similarities are restricted to pain and radio-graphical changes seen within the joint. This review of the literature will unpack key concepts by defining KOA and show how it has evolved over time. The review will also examine the pathophysiology, clinical features, aetiology, diagnosis, and prevalence of the condition. Furthermore, this chapter discusses the various management protocols in the treatment of KOA, specifically in relation to exercise and LLLT as option for management (Arden, Blanco and Cooper, 2015).

2.2 History and Background on the Definition and diagnosis of KOA

Table 1 displays a summary of the definition and therefore the diagnosing criteria of KOA and how it has evolved. KOA was initially defined and diagnosed as a joint disorder involving structural pathology of the joint. The definition and diagnosis of KOA progressed to include structural and functional alterations.

TABLE 1: REVIEW OF THE DEFINITION AND DIAGNOSIS OF KOA (1986-2016)

AUTHOR / YEAR	DEFINITION AND DIAGNOSIS OF KOA
Altman *et al.*, (1986)	KOA is an arthritic condition encompassing joint pain, stiffness and reformed movement patterns at the joint and its associated tendons, cartilage and muscular structures. The condition is therefore defined as a slow progressing; chronic disorder which if left untreated ultimately leads to joint failure.
Hutton (1989); Massardo *et al.*, (1989)	Authors defined KOA by their earlier classification encompassing joint pain, however authors included the damage of articular cartilage together with the remodeling of the joint's articular surface, osteophyte formation, ligamentous change, weakening of associated musculature and synovial alterations due to an imbalance between joint breakdown and repair.
Chaisson *et al.*, (2000)	Over the next decade the definition remained constant as an entire joint pathology together with an imbalance in the joint equilibrium. At the turn of the century however authors then defined KOA not only by its pathological features but added patient history and patient examination markers once the patient had presented with joint pain.

Hernández-Molina *et al.*, (2003); Felson *et al.*, (2003)	The definition began to evolve by including the progression of abnormal joint mechanics due to the excessive load across the knee joint leading to an intra-articular joint pathology.
Sharma *et al.*, (2001); Joern, Schlüter-Brust and Eysel, (2010); Chung *et al.*, (2012)	A few years' later authors once again highlighted the component of joint equilibrium as a primary step in the definition of KOA. Furthermore, authors highlighted that for the diagnosis of KOA patients should exhibit intra-articular structural pathology including cartilage loss, meniscal damage, bone marrow lesions and synovitis.
Javaid *et al.*, (2012; Litwic *et al.*, (2013)	The definition in terms of diagnosis of KOA five years ago included; abnormal joint pathology together with history of additional disease co-modalities, pain-processing factors and noting relevant incidence in the patient's medical history and patient pain and discomfort levels.
McAlindon *et al.*, (2014); Skou *et al.*, (2015)	A degenerative disorder involving the cartilage and surrounding tissue of synovial joints.
Musumeci *et al.*, (2016); Roos and Arden, (2015)	The definition has evolved and is documented as a progressive-degenerative disorder resulting in the deterioration and loss of articular cartilage and surrounding tissue of the synovial joint together with entire joint structural and functional changes, including the synovium, meniscus, ligaments, and bone.

Table 1 can be summarised by highlighting the contemporary definition and diagnosis criteria of KOA as the progressive loss and of articular cartilage, with both structural and functional alteration encompassing the entire joint and its associated ligamentous, bone and muscular structures (Musumeci *et al.*, 2016).

2.3 Pathophysiology of KOA

The physiological processes in the development of KOA is due to interplay of systemic and local factors (Zhang, 2010). These factors include advancing age, genetics, trauma, malalignment of the joint, abnormal joint biomechanics due to factors such as obesity, altered bone density and a disparity in physiological progression (Zhou *et* al., 2014). Figure 2 shows the endogenous predisposition to KOA and the external risk factors influencing the onset of the disease (Heidari, 2011). This results in symptoms such as persistent knee pain, morning stiffness, crepitus, bony tenderness, joint inflammation and reduced knee functionality (Palazzo *et al*., 2016; Zhang *et al*., 2009).

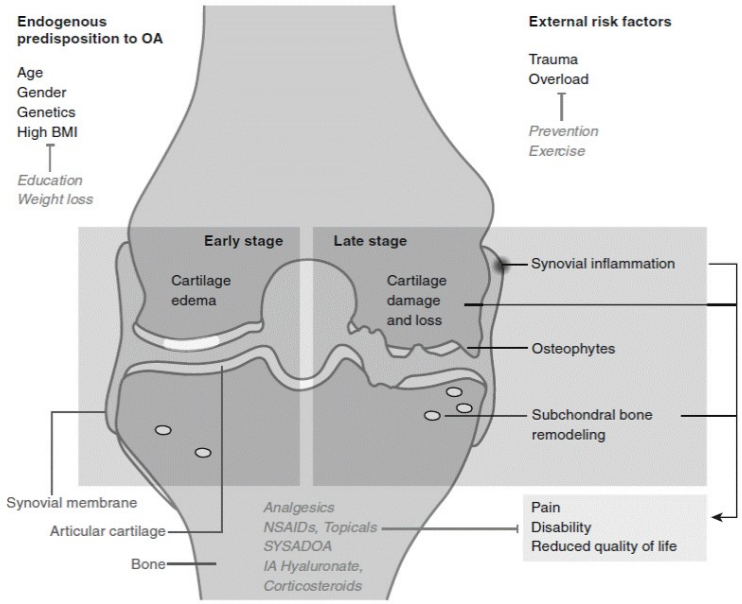


FIGURE 2: PATHOPHYSIOLOGY OF THE OSTEOARTHRITIC KNEE

(Heidari, 2011)

2.4 Clinical Features of KOA

There are numerous clinical features associated with KOA, including joint pain and tenderness, decreased functionality and joint stiffness, crepitus and malalignment of the knee joint (Musumeci *et al.*, 2016). Joint pain and tenderness range from severe to barely noticeable, with KOA patients reporting an increase in pain with activity and decrease with rest. Patients diagnosed with KOA report tenderness on joint palpation with increased sensitivity at the medial and lateral epicondyles of the knee joint (Kazis, Meenan and Anderson, 1983; Musumeci *et al.*, 2016).

There is a gradual progression of KOA symptoms exacerbated by a sedentary lifestyle and aging which often results in decreased functionality and joint stiffness (Heidari, 2011). Studies appear to support the notion that knee stiffness is attributed to

decreased inter-articular joint space and this leads to articular joint friction (Felson *et al.*, 2003). Joint stiffness is exacerbated by extended periods of sedentariness (Soni *et al.*, 2013).

Intra-articular friction can also result in crepitus (Zhang, Nuki and Moskowitz, 2010), thus limiting ROM and functionality (Chung *et al.*, 2012). Studies have shown that these two factors can be improved through physical exercise therapy, with a focus on sustained muscle integrity and joint mobility (Koele *et al.*, 2014).

2.5 Aetiology of KOA

There are two classifications for KOA, namely primary (or idiopathic) or secondary (Fischgrund, 2009). Idiopathic KOA results from an unknown origin, but is usually associated with the older population, signifying a natural decline in joint integrity (Peat, Mccarney and Croft, 2001). Secondary KOA is associated with acute trauma, injury, repetitive motion, congenital conditions and underlying pathologies such as abnormal joints at birth; systemic metabolic diseases, such as vitamin deficiencies; endocrine diseases, such as diabetes; bone dysplasia, and gout (Palazzo *et al.*, 2016).

2.6 Epidemiology of Knee Osteoarthritis

In the literature on the epidemiology and prevalence of KOA, there seems to be a general agreement, both nationally and internationally that, the burden of KOA is high, as joint stiffness and pain often lead to altered levels of functionality and increased disability (Blagojevic *et al.,* 2010; Usenbo *et al*., 2015).

Cross *et al.*, (2014) wrote that KOA was ranked as the eleventh highest contributor to global disability. Years of life with disability (YLD's) for KOA increased from 10.5 million in 1990 to 17.1 million in 2010. KOA is reported to be the tenth leading source of global non-fatal burden of disease, a major course of disability in the elderly and therefore a key public health concern internationally (Quintana *et al.*, 2006).

The United Nations and the World Health Organization (WHO), highlighted that, with an increase in the number of aging populations together with unhealthy lifestyle changes throughout the world, the epidemiology of KOA is predicted to increase dramatically (Pfleger, 2007). This was substantiated years later by Cross *et al.*, (2014) and Briggs *et al.*, (2016), who reaffirmed that conditions such KOA are a major burden on patients, health systems and society, with an increase in prevalence rate.

Authors Litwic *et al*., (2013), highlighted that prevalence of KOA is dependent on factors such as gender, ethnicity, population and the definition used in the classification of the disorder. Therefore estimating true epidemiology is often complex. However, the incidence of KOA increases with age and gender, with a plateau reached after 80yrs of age (Litwic *et al.*, 2013). The prevalence of symptomatic KOA in adults >60yrs is reported to be 10% male and 13% female (Zhang, 2010), other studies report a ratio of between 1.5:1-4:1 between males and females (Litwic *et al*., 2013). A publication by Bijlsma and Knahr, (2007) reported a 15.6% and 30.5% prevalence rate in men and women over the age of 55 years respectively. Within a South African setting, Solomon, Beighton and Valkenburgt, (1975) reported a 60% KOA prevalence

in African males and 48% in African females, compared with a prevalence of 55% in males and 63% in females in a similar Caucasian population. However, Usenbo *et al*., (2015) report a prevalence rate of 33.1% in a rural South African setting and a prevalence of 55.1% in an urban setting amongst adults aged over 65 years.

A study by Haq and Davatchi, (2011) reiterated that the prevalence of KOA was higher in urban populations than in rural populations reporting a 3.3% incidence rate in a rural setting and a 5.5% incidence rate in an urban setting. A publication by Fransen *et al.*, (2011) on a non-Caucasian demographic reported a three times higher KOA incident rate when compared to Caucasian counterparts. The findings of this report should be considered when reporting epidemiology due to population variation both in a South African context and in an international context.

The literature on the prevalence and epidemiology of KOA in an African setting, emerging from Chopra and Abdel-Nasser, (2008) and Usenbo *et al.*, (2015) concludes; that there is an absence of prevalence data on arthritis in Africa. The current PhD review highlights that available reports are too outdated to reflect the present tendencies of the disease. However, the World Health Organization's (WHO) Global burden of disease 2010 publication highlighted that, with Africa's attention on infectious disease and child and maternal health, the burden of non-communicable diseases has amplified (Cross *et al.*, 2014).

2.7 Selected Management Modalities for Knee Osteoarthritis

The goal of KOA treatment is to alleviate the symptoms and slow the progression (Joern *et al*., 2010). The management of KOA should follow a spectrum of management modes form physical exercise therapy to surgical intervention in non-responsive patients (Joern *et al*., 2010). Another publication by Felson *et al.*, (2000), highlighted that the treatment regimen for KOA should aim at controlling pain, improving the function of the joint and patient re-education, thereby serving to improve functional activities of daily living. These authors re-iterated that the treatment regimen should follow an order that consists initially of non-pharmacological interventions, in the form of alternate stand-alone or combinative therapies, followed by pharmacological treatments and then surgical intervention, if conservative management does not work (Joern *et* al., 2010).

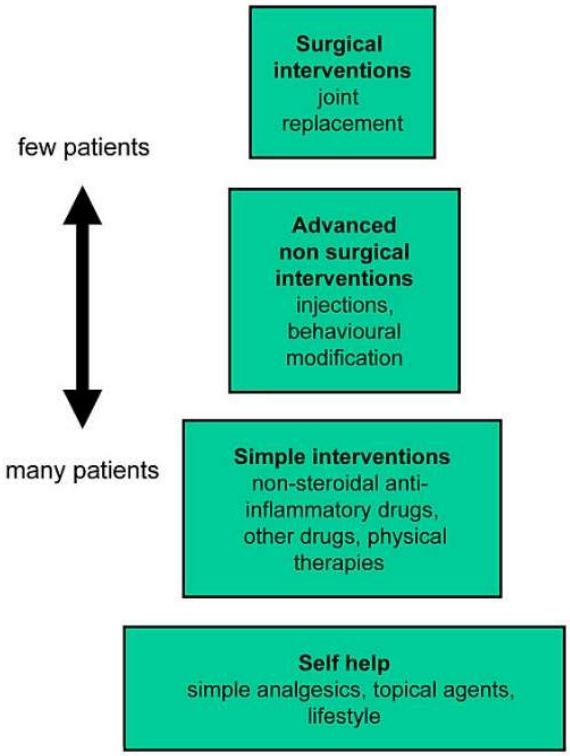


FIGURE 3: OSTEOARTHRITIS MANAGEMENT PRINCIPLES

Adapted from Dieppe and Lohmander, (2005)

Alternative or allied therapies reduce pain and improve joint function in patients with KOA (Adams, Poole and Richardson, 2006; Reid *et al.*, 2010). The next section explores various management modes in the treatment of KOA.

TABLE 2: SUMMARY OF SELECTED KOA MANAGEMENT MODES

CATEGORY	THERAPY TYPE	Author (s)	DEEMED EFFECTIVENESS
Non-invasive therapies	Physical exercise (land based)	Fransen *et al.*, (2015)	Improves muscular, strength, endurance and flexibility of muscles around the knee joint.
	Physical exercise (water based)	Dinesh Bhatia, Tatiana Bejarano, (2013)	Positive results in the management of pain and functionality symptoms by improving strength and flexibility.
	LLLT	Alghadir *et al.*, (2014)	Effective in the management of symptoms related to KOA.

	Allied therapies (massage, ultrasound, TENS)	Walach, Güthlin and König, (2004)	Improves pain and functionality by enhancing blood flow and metabolism thereby reducing the substances involved in pain production.
	Nutritional alterations	Hafsi *et al.*, (2019)	Decreases symptoms of KOA with the possibility of eliminating or delaying invasive measures.
	Podiatry, bracing and taping	Silverwood *et al.*, (2015)	No clinical evidence on disease progression but aids in minimizing reaction forces.
Invasive therapies	Arthroscopic leverage and debridement	Laupattarakasem *et al.*, (2008)	Conflicting evidence on the use of debridement for the effective management of KOA symptoms.
	Knee osteotomy	Ronn *et al.*, (2011)	Effective treatment mode in the management of KOA by increasing weight

			bearing tissue in the joint.
	Arthrodesis	Knops *et al.*, (2009)	Fusion of the joint resulting in increased weight bearing of the joint.
	Total knee replacement	Skou *et al.*, (2015)	Total replacement of the joint, thereby improving patient functionality.
Pharmacological therapies	Acetaminophen	Tanveer *et al.*, (2006)	Used as the 1st line of prescription for the treatment of mild to moderate pain associated with KOA.
	Glucosamine	Kongtharvonskul *et al.*, (2015)	Shows significant improvements in pain score but does not decrease the risk of adverse effects and does not have a clinically relevant effect in slowing progression of joint space narrowing.

	Non-steroidal anti-inflammatory drugs (NSAID's)	Ringdahl and Pandit, (2011)	Provide superior efficacy when compared to acetaminophen and is effective in relieving pain and improving mobility.
	Cox-2 inhibitors	Abate *et al.*, (2010)	Result in significant reduction of pain, improving physical function and benefiting quality of life for pain relief.
	Opioid's	McAlindon *et al.*, (2014)	Considered for patients with severe pain, pain-related functional impairment or those who do not respond to other measures.
	Tropical therapies	Hassett and Williams, (2011)	Used for symptomatic relief, with reduced risk of gastrointestinal complaints.

Joint lubricant and cartilage transplants		Abate *et al.*, (2010)	Complex and expensive procedures, with limited clinical data supporting their efficacy.
Regenerative medicine	Stem cells	Pas *et al.*, (2017)	Minimally invasive procedure resulting in decreased joint inflammation and an improvement in cartilage repair.
	Platelet rich Plasma (PRP) therapy	Patel *et al.*, (2013)	Improved efficacy when compared to saline in pain and functionality markers.

2.7.1 Non-invasive therapies

There are recognised treatment modalities for the management of symptoms related to KOA, including massage, ultrasound therapy and transcutaneous electrical nerve stimulation (TENS), diet modification, relaxation therapy, podiatry, bracing and taping.

Massage therapy

Massage therapy is a prevalent management option for KOA, but its efficacy is ambiguous. However, the mechanism of action includes diminishing and improving

symptoms related to KOA (Lewis and Johnson, 2006). The mechanism of action includes; enhancing blood flow and metabolism thereby reducing the substances involved in pain production (Walach, Güthlin and König, 2004). Massage therapy aids circulation, improves lymph flow of muscles related to the knee joint, such as the quadriceps, hamstrings, abductors and adductors therefore enhancing joint flexibility, and relieving pain (Field, 2014).

Ultrasound therapy and transcutaneous electrical nerve stimulation (TENS)

These therapies are commonly used as alternative, non-invasive management modes for the symptoms of KOA, such as pain and inflammation (Ahsin *et al*., 2009). Ultrasound therapy uses ultrasound waves whereas TENS uses an electrical current with a frequency between 10Hz to 150 Hz (Ahn *et al.*, 2008). The use of ultrasound and TENS enhances pain relief and is more effectively used as a combinative therapy mode (Ahsin *et al*., 2009). Research has shown a significant improvement in dynamic balance and gait when combined with physical activity interventions (Maeda *et al.*, 2017).

Nutritional alterations

Nutritional guidelines include increasing the intake of foods high in omega 3 fatty acid. This had been documented to show an improvement in KOA symptoms as it is linked with reduced joint inflammation, pain and stiffness. Foods high in omega 3 fatty acids reduce levels of two proteins called the C-reactive protein (CRP) and interleukin-6, that cause inflammation, thereby decreasing joint inflammation (Grygorieva and Povoroznyuk, 2009). Furthermore research by Speetzen, (2018) indicates that an

anti-inflammatory diet, which is a diet rich in anti-oxidants, decreases symptoms of OA with the possibility of eliminating or delaying invasive measures.

Podiatry for KOA

Increased joint loading results in an increased risk for KOA. In patients with medial compartment KOA, insoles and footwear have shown to reduce knee adduction moment, however no clinical evidence exists on slowing disease progression (Silverwood *et al.*, 2015). Walking in shoes increases joint load compared with walking bare feet. Flexible shoes with a flat or low heel may be optimal as they promote foot mobility and variable stability. In-soles and foot wear offer great potential, as a simple, inexpensive treatment strategy, for KOA (Bennell and Hinman, 2011). However additional research is required on efficacy and subgroup responsiveness (Silverwood *et al.*, 2015).

Bracing and taping

Bracing and taping are management tools applied with the aim of realigning the patella and unloading soft tissues, thereby reducing pain (Blagojevic *et al.*, 2010). Therapeutic knee tape is a simple, inexpensive, conservative management tool (Beaudreuil *et al.*, 2009). Whilst effective in immediately reducing pain (Adams, Poole and Richardson, 2006), the research is not strong with regards to a significant impact on the observed disability associated with the disorder.

2.7.2 Pharmacotherapy

Patients diagnosed with OA are usually prescribed analgesics to treat pain and inflammation (Abate *et al*., 2010). Pharmacologic treatments vary and may include acetaminophen, oral non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) selective inhibitors, topical analgesics, intra-articular therapies, duloxetine, glucosamine sulphate and chondroitin sulphate (Castaneda *et al*., 2010). However, this management tool does not address joint function, disease modification or increased patient functionality (Cheng and Visco, 2012).

Acetaminophen

Acetaminophen is used for the treatment of mild to moderate pain associated with KOA, acetaminophen or paracetamol is often prescribed as the initial pharmacotherapy mode due to its safety, efficacy and decreased gastrointestinal effects (Tanveer *et al.*, 2006).

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAID's) provide superior efficacy when compared to acetaminophen and is effective in relieving pain and improving mobility (Ringdahl and Pandit, 2011; Cheng and Visco, 2012). The NSAID's category includes drugs such as glucosamine and Diacerin. In a study by Kongtharvonskul *et al.*, (2015) glucosamine showed improvement in pain scores however there was no decrease in disease progression as shown by clinically relevant markers such as joint space narrowing and therefore, does not have a clinically relevant effect in slowing progression of KOA. Whereas drugs containing Diacerein, have a higher risk of adverse GI events when compared to glucosamine. Diacerein also has no clinically

relevant effect in delaying progression of joint space narrowing, in OA of the knee. When compared to Diacerein, glucosamine is the better treatment choice for OA of the knee (Kongtharvonskul *et al*., 2015). Non-steroidal anti-inflammatory drugs do not differ in efficacy and have comparable dose-dependent increases in risk of serious gastrointestinal, renal and cardiovascular events, and therefore are prescribed for the shortest duration at the lowest effective dose (Zhang *et al*., 2009).

COX-2 inhibitors

COX-2 selective inhibitors are superior in efficacy to acetaminophen and comparable to nonselective NSAIDs, resulting in significant reduction of pain, improving physical function and benefiting quality of life for pain relief (Chappell, Desaiah and Liu-Seifert, 2011; Abate *et al.*, 2010).

Opioids

Opioids are considered for patients with severe pain, pain-related functional impairment or those who do not respond to other measures (McAlindon *et al.*, 2014). Codeine, hydrocodone or oxycodone is prescribed for moderate to severe pain. Other commonly used opioids are morphine, hydromorphine and methadone. There are an array of side effects including constipation, nausea, postural hypotension, itching, urinary retention, cognitive impairment, drowsiness, confusion, hallucinations, and vertigo together with a high incidence of addition to the therapy mode (Corsinovi *et al.*, 2009)

Topical therapies

Topical therapies are often used for symptoms related to KOA, with reduced gastrointestinal complaints and improved efficacy and safety (Hassett and Williams, 2011). However, there is a higher risk of dermatologic adverse events such as skin dryness or rash (Hassett and Williams, 2011). Diclofenac, capsaicin, salicylates, piroxicam, buprenorphine and ketoprofen are commonly used as topical therapy (Tugwell, Wells and Shainhouse, 2004).

Joint Lubricants

Joint lubricants and cartilage transplants have gained popularity for KOA treatment. However, these procedures are complex, expensive and have limited clinical data supporting their efficacy (Abate *et al.*, 2010). Two different types of local intra-articular therapies are available, i.e. corticosteroids and hyaluronates. Intra-articular corticosteroid produces short-term pain relief and reduces inflammation and joint effusion (Zhang, 2010). Hyaluronic acid is a physiologic component of the synovial fluid and is reduced in KOA, therefore intra-articular injection of hyaluronic acid, can restore the typical articular balance (Abate *et al.*, 2010). Following the use of pharmacotherapy without the desired outcome, surgical interventions are considered as the next step of treatment.

2.7.3 Surgical intervention

Surgery is indicated when the patient's symptoms accord with the physical and radiological findings and all conservative treatments have been exhausted. The type

of surgical procedure depends on the age of the patient, gender, weight, level of physical activity, degree of joint damage (Ronn *et* al., 2011). There are four surgical interventions commonly performed as a surgical management protocol for the KOA patient; i.e. arthroscopic lavage and debridement, knee ostomy, arthrodesis and a total knee replacement, which will be explored in this section.

Arthroscopic lavage and debridement

Arthroscopic lavage and debridement of the knee involves the visually guided infiltration of saline solution into the knee joint with the simultaneous removal of fluid, with the intent of extracting any excess fluids and loose bodies thereby smoothening of the bone surfaces (Knops *et al.*, 2009). In a publication by Laupattarakasem *et al.*, (2008) the authors identified conflicting evidence in the use of debridement for KOA. After analysing 3 RCT's with a total of 271 KOA patients the conclusion drawn was that there is "gold" level evidence that debridement is not a beneficial management strategy for KOA. However, authors Felson, (2000) and Ronn *et al*., (2011) have indicated that arthroscopic lavage is an effective option for younger and middle-aged KOA patients. Reviewing publications in in this field of therapy lends to the conclusion that this mode of intervention should be considered on an individual basis.

Knee osteotomy

Knee osteotomy refers to realignment surgery by cutting the bone to correct knee alignment and is especially useful in patients with unilateral KOA (Brouwer *et al.*, 2014). The goal is to shift weight from the damaged knee joint to the unaffected joint. The two common types of osteotomies are Tibial (reshaping tibia) and femoral

(reshaping the femur). While this procedure is effective greatest quality of life benefits are noted in patients who underwent appropriate physical exercise therapy post intervention (Ronn *et al*., 2011; Egloff, Hügle and Valderrabano, 2012).

Arthrodesis

Arthrodesis, or joint fusion, is a procedure used to fuse together bones in the knee joint, allowing the joint to bear more weight thus increasing joint stability (Van Rensch *et al.*, 2014). Arthrodesis is considered in patients with KOA instability and severe pain markers. Evidence has reported that there is a decreased fusion rate with increased bony defects (Felson *et al.*, 2000).

Total knee replacement

Total knee replacement is recommended in advanced KOA (Ronn *et al*., 2011). The prosthesis durability should be considered due to lifespan recommendations of 15-20 years (Knops *et al.*, 2009). Through total knee replacement surgery, the pain and disability associated with KOA is addressed, restoring patient's functionality and quality of life. Complication of total knee replacement surgery should be considered and often include prosthesis mechanical deformation, continued pain, infection and joint stiffness (Skou *et al.*, 2015). With the progression and development of therapeutic medicine, regenerative medicine in terms of stem cell therapy and Platelet Rich Plasma (PRP) is periodically considered as a management mode for the KOA patient.

2.7.3. Regenerative medicine

Regenerative medicine aims to promote healing through minimally invasive methods of treatment to slow the progression of KOA (Vaishya, 2019). This branch of treatment relies on strengthening membrane barrier function, supporting endothelial adaptively and enhancing cellular uptake and nuclear signalling systems (Hafsi *et al.*, 2019). Common regenerative medicine modes discussed in this thesis will be stem cell injections and Platelet Rich Plasma (PRP) therapy.

Stem cell injections

This procedure is a minimally invasive procedure resulting in a decreased in inflammation and an improvement in cartilage repair(Pas *et al.*, 2017). Stem cell injections have found to be effective in reducing pain and improving functionality, without hospitalization and shows clinical improvements in cartilage quality (Koh and Choi, 2012; Koh *et al.*, 2013; Orozco *et al.*, 2013).

Platelet Rich Plasma therapy (PRP)

Platelet rich plasma is known as autologous conditioned plasma which is derived from human blood and centrifuged to remove the red blood cells (Khoshbin *et al.*, 2013). In a randomised controlled trial (RCT) by (Patel *et al.*, 2013) the authors found that a PRP injection showed improved efficacy when compared to saline in pain and functionality markers.

Each of the treatment modes investigated above have shown advantages and disadvantages. Recognised non-surgical intervention and pharmacotherapy modes address symptoms of short term pain relief, without much impact on functional effectiveness. Surgical interventions address symptoms of pain and inflammation together with restoration on functional living, however there are restrictions with regards to costs, prosthesis lifespan together with persistent pain post intervention. With the inclusion of regenerative medicine, therapy is less invasive addressing the physiological cellular functioning associated with KOA. However, effectiveness should include addressing the structural and functional components associated with KOA therefore, this thesis set out to explore the effectiveness of physical exercise therapy and LLLT used either in isolation or as a combined therapy mode for the management of KOA.

2.8 Exercise as a Management Tool for Knee Osteoarthritis

Physical rehabilitation is widely recommended for managing KOA (Johnson and Bulkow, 2005; Bjordal *et al.*, 2007). These include modes such as land exercises and aqua therapy, strength training, flexibility training, and the participation in social sporting activities (Palazzo *et al.*, 2016). Biomechanical factors, such as reduced muscle strength and joint malalignment, have an important role in the initiation and progression of KOA, therefore employing exercise or physical rehabilitation results in improved muscle function (Grotle *et* al., 2008). By comparison, superiority of exercise mode in the symptomatic management of KOA cannot be established and recommendations on using either land or water-based exercises are dependent on patient safety, preference and efficacy (Stemberger and Kerschan-Schindl, 2013; Ageberg and Roos, 2015). Balneotherapy, also known as hydrotherapy aqua therapy

involves physical exercise in a temperature controlled pool and showed positive results in the management of pain and functionality symptoms of KOA by improving strength and flexibility (Bhatia and Bejarano, 2013). Majority of the consensus on physical rehabilitation for KOA concludes that rehabilitation should begin with aerobic and endurance conditioning, followed by flexibility, strength and functional activities (Grotle *et* al., 2008; Stemberger and Kerschan-Schindl, 2013; Fransen *et al.*, 2015).

With regards to the various component of fitness; strength training is important in patients with KOA to restore functionality, balance and address deficits in lower limb loading (Ciolac and Greve, 2011). A combined approach utilising concentric and eccentric strength exercises is shown to be more effective than isometric exercises (Kumar, 2015). Flexibility training has been shown to improve symptoms of pain, gait, anxiety, and fear of falling (Cheung *et al.*, 2016). Aerobic or cardiovascular component of fitness, be it either land or water based training, has shown to improve patient functionality, physical fitness and muscular strength making the patient more functional and active (Bennell and Hinman, 2011). Authors Pisters *et al*., (2007) have reported that while both land and water-based activity is beneficial to the KOA patient, water-based exercise results in greater adherence to exercise and decreased impact on the knee joint when compared to a walking based exercise regimen.

Exercise adherence has been identified as a predictor in long term accomplishment of physical functionality (Bennell and Hinman, 2011). It is therefore important for practitioners to identify adherence trends amongst the patients for optimal efficacy. Majority of patients report financial and logistical constraints as key indicators for

cessation of a therapist led physical rehabilitation protocol. A study by Pearson *et al*., (2016) on the use of web based physical rehabilitation tools (i.e. Apps, websites and online physical therapist platforms) concluded that these management tools, are of great benefit as they provide the patient with an easily accessible, low cost management tool thereby promoting exercise adherence.

2.9 Low Level Laser Therapy

Low Level Laser therapy (LLLT) is a therapeutic class 3b laser and is classified as a non- thermal modality, meaning that these modalities do not raise the subcutaneous tissue temperature greater than 36.5ºC (Brosseau, 2005; Alfredo *et al*., 2011). Therefore, the therapeutic effects of LLLT is photochemical. As a result, when light (photons) enter the human cell at the point of application, chromophores molecules become active, and trigger a photochemical reaction that leads to the desired physiologic effect (Baxter, 1994; Baxter, Bleakley and McDonough, 2008).

LLLT has been used in medicine since the early 1960's when its efficacy for the management of open wounds, reduction of pain and inflammation was discovered (Mester, Mester and Mester, 1985; Mester and Mester, 2017). It has since evolved to include light emitting diodes and a light source including both red and infra-red wavelengths with a range of 1mW – 500mW (Cheung *et al.*, 2016). This type of laser therapy is also known as photobiomodulation therapy, phototherapy, cold laser therapy and low intensity laser therapy (Mester and Mester, 2017).

2.9.1 Mechanism of low level laser therapy

Photobiology highlights the effects of LLLT at a cellular level. This thesis looked at 17 key publications reporting on the mechanism of LLLT since its inception to present day publications. The First Law of Photochemistry states that: light must be absorbed for photochemistry to occur. The Second Law of Photochemistry is related to the absorption spectrum, which is a plot of the probability that light of a given wavelength will be absorbed by the system under investigation. Each chemical compound has a different absorption spectrum, because of its unique electronic structure. Each of the wavelengths absorbed by a chemical compound will be absorbed to different degrees, due to the unique electronic structure of each physiological compound. The third law of photochemistry is considered once a photo-biological response is detected. In order to produce the desired effect, factors around wavelength and dose of radiation should be considered. Therefore, an action spectrum is a plot of the relative effectiveness of different wavelengths of light in causing a biological response. Thus, an action spectrum not only identifies the wavelength(s) that will have the maximum effect with the least dose of radiation, but it also helps to identify the target of the radiation (Bjordal, 2012; Mester and Mester, 2017).

Drawing a parallel between photobiology and cellular function highlights the mechanism of LLLT. To explain, in a normal functioning cell, a terminal enzyme called cytochrome C oxidase transports oxygen (O_2) with Nicotinamide adenine dinucleotide (NADH) to form hydrogen ions. When the cell is compromised during sickness, injury, stress or aging, the mitochondria start producing nitric oxide (NO) which competes with O_2 binding to the cytochrome C oxidase, displacing the O_2 and preventing the production of adenosine triphosphate (ATP) due to an increased oxidative stress. This

causes a range of pathologies from inflammation to cell death resulting in symptoms such as pain and inflammation (Smith, 2005, 2010). Applying a low level laser beam breaks the bond between the NO and the cytochrome C oxidase allowing the O_2 to freely bind NADH to ATP. This process potentially decreases the oxidative stress promoting tissue generation, theoretically allowing for a decrease in pain and inflammation at the treated site, thereby improving patient functionality (Bjordal, Lopes-Martins and Iversen, 2006).

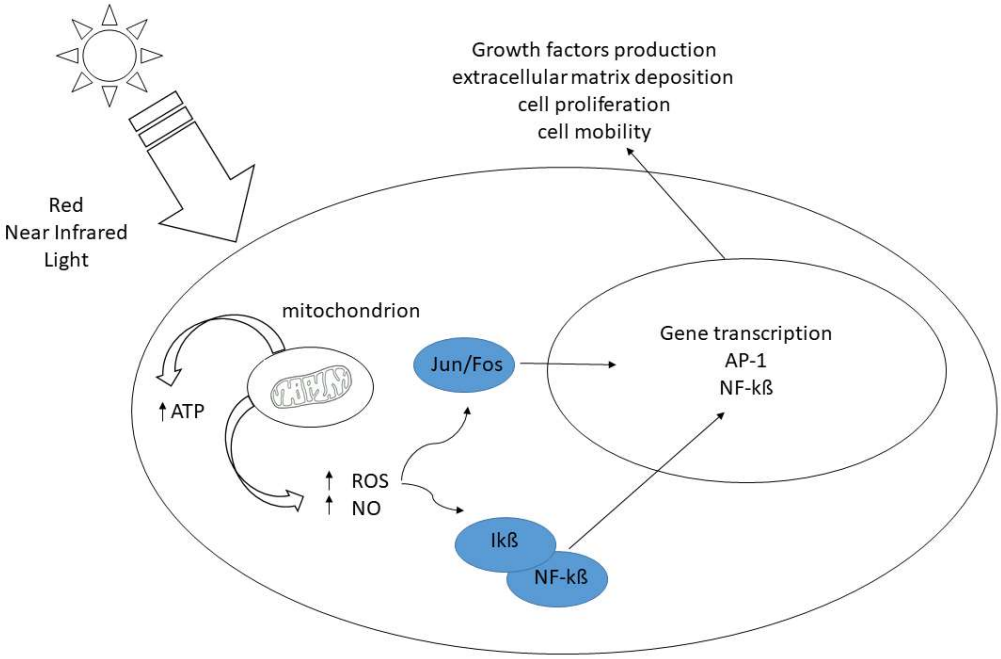


FIGURE 4: MECHANISM OF LOW LEVEL LASER THERAPY

(Bjordal, Lopes-Martins and Iversen, 2006)

Soft tissue injury and pain, releases inflammatory chemicals including prostaglandins, serotonin, histamine, substance P (Lee and Ernst, 2011). The mechanism of pain relief is unclear however, publication have indicated that pain relief is photochemical (Tascioglu *et al.*, 2004; Bjordal, Lopes-Martins and Iversen, 2006; Tascioglu *et al*., 2012). The mechanism of action has been indicated as an inhibition of peripheral

nerve nociceptive signals and a combination of collagen proliferation, and circulation enhancement resulting from LLLT exposure (Gur *et al.*, 2003; Tascioglu *et al*., 2012). This results in an increase in ATP production, redox system enhancement (de Paula Eduardo *et al*., 2010) and an elevated analgesia effect due to inhibition of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2), modulating nerve transmission. These processes result in elevated serotonin and endorphin release (Fulop *et al*., 2010; Abrisham *et al*., 2011).

2.9.2 Laser parameters

Parameters such as wavelength, power output, power density (intensity), and energy density (dose) are key in therapeutic laser efficacy (AlGhamdi, Kumar and Moussa, 2011). Table 3 is an indication of the laser parameters and their functionality.

TABLE 3: LASER PARAMETERS

LASER PARAMETERS	**FUNCTIONALITY**
Wavelength	The electromagnetic wavelength of light comprises of crests and through's and is measured in nanometers (nm). Frequency is defined as the number of oscillations per second and amplitude is difference in wavelength (Rojas and Gonzalez-Lima, 2011). Superficial tissue is treated at wavelength of 600 -700nm and deep tissue at a wavelength of 780-950nm (Chung *et al.*, 2012).

Power output	The power output (mW) is a measure of the energy produced is the amount of energy produced. Research has indicated that higher power output protocols require brief application times (Hawkins and Abrahamse, 2007).
Power density	Power density is defined as power per unit area emitted from the device, measured in mW/cm^2 (Baxter, 1994).
Energy density	Energy density is measured joules per square centimeter (J/cm^2) and is the prescription of laser required. Factors which impact energy density include type of tissue being treated, severity of the condition and pigmentation (Hawkins and Abrahamse, 2007).

2.9.3 Evidence for the effectiveness of LLLT in musculoskeletal conditions

Past studies have produced some important insights into LLLT; however, this modality remains controversial with regards to methodology and prescribed wavelength (Bjordal *et al*., 2008; Rayegani *et al.*, 2017). A synthesis of data on the safety and effectiveness of LLLT in the management of KOA was compiled by Rayegani *et al.*, (2017) reporting that laser parameters are important in computing and reporting the effectiveness of this mode of therapy. Clinical trials have reported positive effects in the treatment of chronic pain conditions such as rheumatoid arthritis (Johannsen *et al*., 1994; Juhl, 2006) and fibromyalgia (Gur *et al*., 2002a; Gur *et al*., 2002b; Panton *et al*., 2012). Positive results have also been reported in treatment of lumbar (Gur *et al.*, 2003), cervical (Gur *et al*., 2003; Chow, Heller and Barnsley, 2006) and painful musculoskeletal pathologies; (Gam, Thorsen and Lonnberg, 1993; Krasheninnikoff *et al*., 1994; Alghadir *et al.*, 2014). Pain and structural alterations have been documented

in the treatment of lateral or medial epicondylitis (Bjordal *et al*., 2008), plantar fasciitis (Basford *et al*., 1998), and myofascial pain (Thorsen *et al*., 1992; Gam, Thorsen and Lonnberg, 1993). In a study by Trelles *et al*., (1994), the researchers found that LLLT reduces KOA pain and improved circulation.

There are numerous aspects to consider regarding the inconsistent reporting with regards to the therapeutic efficacy of LLLT (Basford, 1995; Cotler, 2015; Rayegani *et al.*, 2017). These factors include unstandardized protocols for the treatment of various pathologies, energy density discrepancies between documented reports and the effect of laser-drug interaction (de Paula Eduardo *et al*., 2010; Hashmi *et al*., 2010; Fukuda *et al.*, 2011; Alfredo *et al.*, 2018). In addition to these reasons' authors Hashmi *et al*., (2010) and Rayegani *et al.*, (2017) reported that there is a lack of consensus amongst experts in the field in terms of the mechanisms of action of LLLT at cellular level.

Yousefi-Nooraie *et al*., (2008); AlGhamdi, Kumar and Moussa, (2011) and Alghadir *et al.*, (2014) have shown that the use of LLLT as a co-modality for the management of musculoskeletal pain is feasible. Low level laser therapy and exercise has been used in the treatment of lower back pain and the results demonstrated, that LLLT did not reduce pain more than exercise, therefore suggesting that the two modalities should be used to complement each other (Yousefi-Nooraie *et al*., 2008). Authors, Bjordal *et al*., (2008) recommended that LLLT should be considered as an alternative therapy to NSAIDs and corticosteroid injections in pain management due to the long-lasting effects of LLLT. Recent publications by (Alghadir *et al.*, 2014) concluded that LLLT proved to be an effective treatment in the management of KOA symptoms. These

three studies were used as the basis of the current thesis; hypothesising that this management modes may have a positive effect on patients with KOA.

2.9.4 Exercise and LLLT as co-modalities for the treatment of KOA

Within the field of therapeutic medicine, LLLT has been used for KOA pain management (Gur *et al*., 2003; Abrisham *et al.*, 2011; Alfredo *et al.*, 2018; de Matos Brunelli Braghin *et al.*, 2018) as it stimulates reparative properties in joint cartilage (Alfredo *et al*., 2011), aiding in the structural benefits of employing this treatment mode for the treatment of KOA. Therefore, the combination of physical exercise and LLLT may be more effective from a structural and functional rehabilitative point.

Early combination studies by Bülow, Jensen and Danneskiold-Samsøe, (1994) to evaluate the effect of laser on chronic pain of KOA, found no significant differences between the LLLT and placebo group in terms of analgesic requirements and level of pain. However, effect sizes in terms of quadriceps strength and palpation tenderness were greater in the LLLT group.

Bjordal *et al*., (2003) demonstrated that global health status improved more for patients in the active LLLT groups compared to placebo laser groups. Concluding that LLLT reduced pain and improved health status in chronic joint disorders. Furthermore, Bjordal *et al*., (2006) published a system review of 12 RCT's concluding that laser therapy reduced joint pain and improved functionality when compared to a placebo intervention. The review culminated by stating that there is moderate-quality evidence

that LLLT reduces pain and improved patient functionality due to flaws or inconsistencies in methodology.

Fukuda *et al.*, (2011); Alfredo *et al.*, (2012), (2018) and de Matos Brunelli Braghin *et al.*, (2018) established that there are positive effects of LLLT in combination with a programme of exercise on pain assessed using a visual analogue scale; functionality, using a questionnaire; ROM, using a goniometer; muscular strength, using a dynamometer and quality of life in patients using a Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) questionnaire. The data was collected as a cross sectional study design, with a pre and post-test together with relevant intervention strategies.

Therapeutic medicine has evolved into a multi-practitioner approach to treating a patient. There is increased research around combinative therapies for the management of KOA. A study by (de Matos Brunelli Braghin *et al.*, 2018) reported that while there is a difference in gait patterns amongst patients with KOA, the combinative approach (using exercise and LLLT) provides physical rehabilitation practitioners a mode of therapy to improve pain and functionality, while addressing gait pattern limitations in this cohort of patients, therefore resulting in an improvement in quality of life.

2.10 Summary

In this chapter, it has been shown that KOA is a multi-faceted non-curable condition with varied aetiology; therefore, the goal of treatment is to alleviate the symptoms and

slow the progression. The various treatment modes investigated have shown benefit and complication of use. Physical rehabilitation is widely accepted for the management of KOA in primary care settings. LLLT influences the structural and functional components of KOA by having a positive effect on pain, functionality and ROM, especially when used as a co-modality to exercise.

2.11 Research Gaps

The meta-analysis conducted by Usenbo *et al.*, (2015) reported that OA is the most prevalent form of arthritis, in a South African urban setting at 55.1% and between 29.5% up to 82.7% in a rural setting among adults aged over 65 years. Other results include highest prevalence of 33.1% for KOA in rural South Africa. The data on prevalence of KOA in South African context are limited and not up to date, and this study aimed to bridge the gap in literature by documenting and updating the incidence and treatment profile of KOA.

The current treatment regimen for KOA focusses on pain control, joint function improvement and patient re-education thereby minimising functional incapacity. In addition, and contrary to theoretical prescriptions the most common prescribed treatment mode for KOA is the use of pain medication which has shown unimpressive results and worrying side effects. While pharmacological or surgical interventions may address pain control, they do little in the form of joint function and patient re-education; therefore, the study proposes to address the gap in both structural and functional deficits in the treatment of KOA by using LLLT as a standalone or adjunct treatment with exercise.

CHAPTER 3

3. METHODOLOGY

3.1 Introduction

The objectives of this PhD study were three-fold: i) to investigate the prevalence of KOA in South Africa, using convenience and snowball sampling; ii) to underline a treatment paradigm in order to identify practitioner KOA management protocols; and iii) to conduct an intervention study on the use of exercise and LLLT in isolation or as a co-modality in the management of KOA. This chapter will look at the study design, sampling technique, sample size, data collection, analysis and synthesis for each of the three study objectives.

3.2 Prevalence Study

3.2.1 Study design

The study design employed to gather data on the prevalence of KOA in a South African males and female population, aged 45-75yrs, was a descriptive survey method utilising convenient, snowball sampling (Creswell, 2014). The goal of this objective was to determine the prevalence of KOA within a specific South African cohort based on data from the South African healthcare funders.

3.2.2 Sampling technique and randomisation

An e-mail was sent to the following medical aid scheme providers: Discovery Health, Bonitas, Momentum Health, Medscheme and FedHealth. The data gathered was then used to identify and document the gap in literature regarding the incidence of KOA within a particular South African cohort. A single stage sampling procedure was

employed, and the names of medical aid scheme providers were identified and contacted. These medical scheme providers were contacted to obtain data on KOA claims in one fiscal year using the associated ICD-10 codes (Appendix 2).

3.2.3 Sample size

The five South African medical scheme providers were contacted. One medical scheme was unresponsive, despite numerous attempts for contact, electronically, telephonically and personally. Another medical scheme provider was unable to provide the data as required by the study methodology. Therefore, the remaining three schemes were able to provide the data as requested.

3.2.4 Data collection and analysis

The data gathered from the medical aid scheme company were analysed and reported using frequency tables and descriptive statistics. Statistical analysis was performed using the Statistica v13.3 programme (TIBCO Software., 2017) and Microsoft Excel (Microsoft, 2016). After assessing the normal distribution of the data using the Shapiro-Wilks test. Data is presented as percentage of the population.

3.3 Treatment Paradigm Study

The treatment paradigm study was aimed at evaluating the management protocol used by medical and allied practitioners in the treatment of patients with KOA. This section of the methodology will be discussed in terms of establishing content validity of the circulated questionnaire, study design, sampling technique, sample size, data collection and analysis.

3.3.1 Content validity of questionnaire

The questionnaire was piloted for content, construct validity (Principal component analysis) and functionality. The questionnaire was circulated electronically to 5 academic staff members within the faculty of Health Sciences, 5 general practitioners, 5 allied practitioners and 5 specialist practitioners. There was a 98% response rate. Table 4 tabulates the comments and action from the pilot study.

TABLE 4: PILOT STUDY: QUESTIONNAIRE

QUESTION	PILOT GROUP COMMENT	ACTION
Close ended question	The question was understood well	No alterations were made
Open ended question indicating the most suggested mode of therapy from	A choice should be given or the therapy modes should be stipulated.	Type of question changed to choice question, giving the option of 5 stipulated therapy modes.
Deemed efficacy and compliance	5 point Likert scale was too ambiguous in interpretation. Options provided were agree, strongly agree, neutral, disagree and strongly disagree.	Scale changed to a 3-point scale with options for efficacy; effective, not effective and neutral or no comment and options for compliance; compliant,

		not compliant and no comment.

3.3.2 Study design

A descriptive survey method was used as it allowed the economy of the design and the rapid turnaround time of data collection (Fowler, 2014). This method allowed the study to gather quantitative data from a large population base electronically, as it had the strengths of time saving, cost effectiveness and convenience of data collection on the part of the population (Vogt and Johnson, 2011; Fowler, 2014). To support the study design, a convenient sampling technique was used.

A questionnaire was designed consisting of two close ended questions indicating the percentage of KOA and bilateral KOA patients consulted at the practice; one choice question indicating the most suggested mode of therapy from a choice of pharmaceutical, surgical, homeopathic, physical exercise therapy and LLLT and finally, 3 Likert type scale questions on the deemed efficacy and deemed compliance of the modes of therapy as stated above.

An introductory email sent, explained the purpose of the study, length of the survey, methodology and informed consent. The questionnaire was distributed electronically via an emailed hyperlink to the online survey, using google forms. Informed consent was provided by selecting the link to access the questionnaire. All fields were set up as compulsory and respondents were able to navigate between questions during the data collection process. No personal details such as contact details or practice details

in the form of practice number and address were collected. Questionnaires were distributed to 713 practitioners across South Africa, using a closed survey recruitment process. Details of the practitioners were obtained from a data base housed at a clinical research institute in Johannesburg available to the researcher. The questionnaire was circulated to the database of practitioners once a month for a period of 6 months. Uncompleted questionnaires and non-responders after 6 months of contact were excluded from the study.

3.3.3 Sampling technique

An e mail was sent out to 723 medical practitioners located within Gauteng province, South Africa. These practitioners were identified from a data base issued by a research entity at a local government hospital. This database is available to medical practitioners and is hosted by the research department at the Baragwanath Hospital. Appendix 3 is an outline of the printable version of electronic questionnaire (Deemed KOA management paradigm) sent out. The practitioners on the database included general medicine practitioners, specialised orthopaedic practitioners and allied professions working in the field of healthcare (i.e. physiotherapist, Biokineticists, chiropractors, pharmacists, homeopaths and occupational therapists).

3.3.4 Sample size

The complete list of 723 medical practitioners was contacted via electronic mail. Two hundred and ninety practitioners were unresponsive after six months of regular communication reminding practitioners to fill out the online questionnaire. Practitioners were contacted via e mail monthly for a period of 6 months. Twenty

participants' data were not utilised for the study as they did not complete the entire questionnaire, or they did not work with patients on a daily basis or they did not fall within the stipulated practitioner delineations. The final sample size was therefore n=413.

3.3.5 Data collection and analysis

Once the responses were received, they were analysed using frequency tables and descriptive statistics. Response bias (Fowler, 2014) was taken into consideration by contacting practitioners not on the initial data subset list. Non-responders could not be contacted as responses were anonymous. Once collected, descriptive statistics were used to analyse the relationship between practitioner viewpoints and deemed treatment efficacy, deemed treatment compliance and incidence of KOA in clinical practice. The Pearson's Chi Square statistic was performed using Statistica (TIBCO Software., 2017) to test the relationship between deemed efficacy and deemed compliance of the pharmaceuticals, surgical interventions, homeopathic intervention, exercise therapy and LLLT.

3.4 Intervention Study

The intervention study used a quantitative technique for data collection and analysis. Analysing the relationship between KOA variables and the use of exercise and LLLT used in isolation or as a co-modality. The methodology of the intervention study will be discussed based on study design, sampling technique, sample size, study site, inclusion and exclusion criteria and data collection and analysis.

3.4.1 Study design

The purpose of using a descriptive, intervention study design was to gain insight into the differences between the groups participating in exercise, LLLT, or a combination of the two modalities. According to Creswell, (2014), this type of quasi-randomisation technique minimises differences, that may exist between the experimental and control groups prior to the intervention being employed.

This study employed a factorial design experiment, which is a variation of the between group design experiment (Vogt and Johnson, 2011) as it involved using three intervention variables (i.e. exercise, LLLT, and a combination of the two) to examine the independent and simultaneous effect of the respective treatments on the outcome measures of knee ROM, knee circumference, WOMAC pain scale and physical functionality. This research design allowed the study to explore the effects of each treatment separately, as well as determining the effect on the variables explored, thereby providing a rich and encompassing multidimensional view.

3.4.2 Sampling technique and randomisation

Participants were allocated into either of the intervention groups by using a randomisation technique. Pre-sealed envelopes with the relevant intervention group were attached to each participant's documentation once the initial battery of tests had been completed. These envelopes were created, sealed and allocated by an independent member not directly linked to the study. According to De Vos *et al*., (2002), this method challenged potential threats to the external validity of the selected experimental design.

3.4.3 Sample size

The quantitative study sample size was estimated at 90 KOA patients with alpha set at 0.05 and power set at 85%. For a study comparing three means, the equation used to calculate actual sample size was:

$$n = \frac{(Z\alpha + Z\beta)x^2[2\rho(1-\rho)]}{\delta^2}$$

n = sample size

Where N is the total sample size (the sum of the sizes of both comparison groups), σ is the assumed standard deviation (SD) of each group (assumed to be equal for both groups), the Zα/2 value for the desired significance criterion, the Zβ value is that for the desired statistical power, and D is the minimum expected difference between the two means. These respondents were equally distributed amongst the three different intervention groups (n=40). Participants were grouped into the following three groups; exercise group (n=39), LLLT (n=40), and the combined LLLT-exercise group (n=32). Figure 5 is a diagrammatic representation of the sample size for the duration of the study.

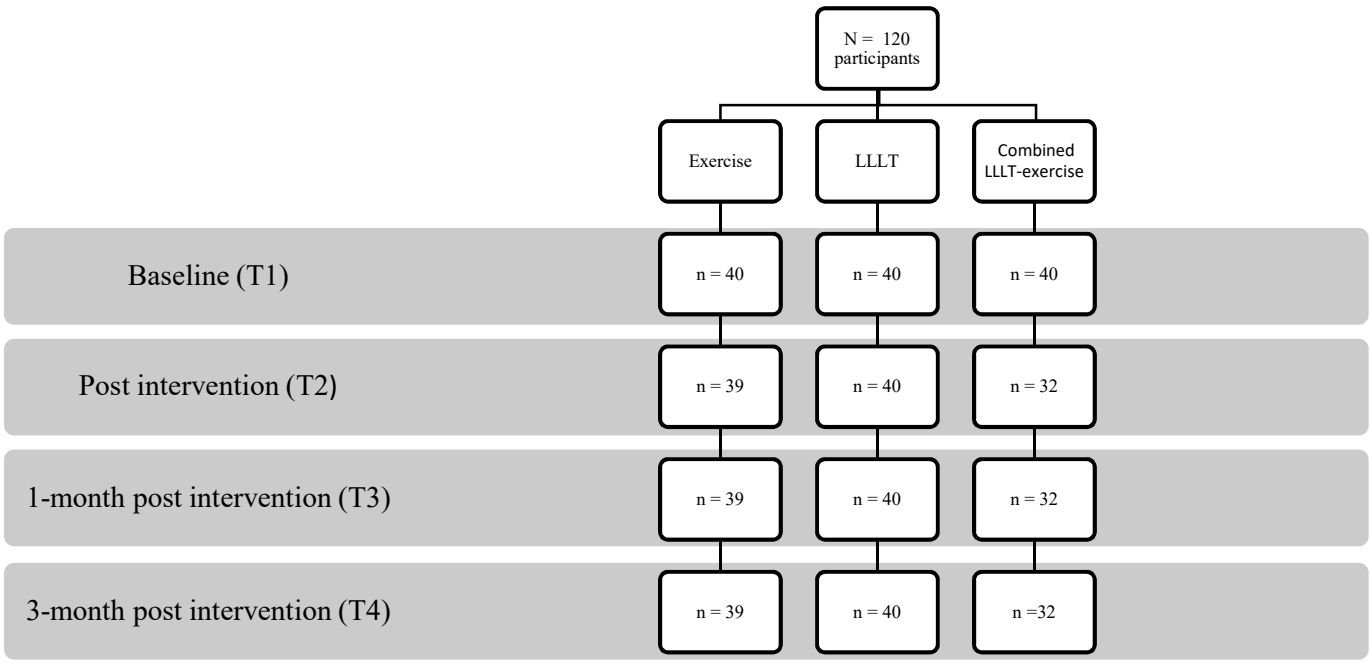


FIGURE 5: INTERVENTION STUDY: SAMPLE SIZE ALTERATIONS

3.4.4 Study site

A private Biokinetics practice, located at Unit 1, 322 Flamingo Street, Lenasia, was used for the data collection. This site was convenient for prospective participants to attend their pre and post intervention testing as well as their respective intervention protocols.

3.4.5 Inclusion and exclusion criteria

3.4.5.1 Inclusion criteria

For study participation, the potential KOA participants were:

- Male or female
- Confirmed KOA diagnosis from a referring medical practitioner
- Between the ages of 40-75 years

3.4.5.2 Exclusion criteria

The following participants were excluded from the study:

- A contraindication or unknown response to LLLT
- Diagnosed with cancer and/or epilepsy
- Individuals who were physically unable to complete one or more tests in the battery of physical tests required for the study were excluded from the study.
- Individuals who were unable to commit to the intervention study

3.4.6 Data collection

Data was collected for knee circumference, pain management, knee range of motion (ROM), and physical functionality at the four time points; pre intervention (T1), post intervention (T2), 1-month post intervention (T3) and 3-months post intervention (T4).

3.4.6.1 Knee circumference

As noted in the literature review chapter, one of the common symptoms associated with KOA is a disproportionate accumulation of joint capsule fluid (Jakobsen *et al*., 2010; Majima *et al*., 2012) and therefore measuring knee circumference is a key indicator for treatment efficacy. Empirical evidence by Sturgill *et al*., (2009) confirms the notion that a measuring tape is a cheap, simple, fast and reliable instrument depicting joint effusion with excellent instrumental reliability scores (Holm *et al*., 2010). Therefore, bilateral knee circumference was measured using a measuring tape with inter-tester variability concerns being addressed as all testing was done by the principle researcher utilising the same plinth, and measuring tape (Jakobsen *et al*.,

2010). As a result, the participant was requested to lie in a supine position; the treated knee was then supported by a towel to create a 30° flexion in the knee to relax the quadriceps muscles. The measuring tape was used to measure the joint circumference proximal (2cm above the mid patella), mid and distal (2cm below the mid patella) to the patella. The data were recorded at all four time points (T1-T4) for each participant to the closest millimetre (mm) (Durstine *et al*., 2009; ACSM, 2016).

3.4.6.2 Pain and functionality management

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is theoretically a self- administered questionnaire, used to describe and evaluate pain and function. This questionnaire was chosen due to validity and reliability of the questionnaire as a valid tool in reporting KOA pain and functionality (Salaffi *et al.*, 2003). Recent studies by Salaffi *et al.*, (2003) and Basaran *et al*., (2010) support the validity and reliability of the WOMAC Osteoarthritis Index on patients with hip or KOA and it was therefore used as the scale of measurement during the current study. This questionnaire was used to describe and evaluate the pain and functional capacity of the participant at all four time points (T1-T4) (Quintana *et al.*, 2006). The WOMAC measures five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68). Physical functioning questions cover everyday activities such as stair use, standing up from a sitting or lying position, standing, bending, walking, getting in and out of a car, shopping, putting on or taking off socks, lying in bed, getting in or out of a bath, sitting, and heavy and light household duties (Salaffi *et al.*, 2003). The change in WOMAC score was used as the variable outcome of pain and functionality during the study. A hard copy was provided to each participant. The data were then transcribed on the electronic version obtained from

the following link: (http://www.orthopaedicscore.com/scorepages/knee_injury_osteopaedic_outcome_score_womac.html). The respective scores were noted accordingly (Appendix 4). An alternate copy was made available in Afrikaans if the need arose. However, all the study participants were well versed in the English language.

3.4.6.3 Knee range of motion

Knee ROM was measured in terms of knee flexion and extension, using a goniometer bilaterally. Once again, inter-tester variability was addressed as all testing was done by the principal researcher utilising the same plinth, and goniometer as recommended by (Jakobsen *et al*., 2010). For flexion measurements the participant was requested to bring the foot as close to the buttocks as possible, without the assistance of the researcher. For extension measurements, the participant was instructed to actively straighten the knee, with both the angles being measured using a Baseline® goniometer recorded to the nearest degree (°) (Durstine *et al*., 2009; ACSM, 2016). Knee ROM was measured at all four time intervals (T1-T4).

3.4.6.4 Physical functionality

In studies by Marshall *et al*., (2015) and Radtke *et al*., (2016), the authors concluded that one minute timed-sit-to-stand test appears to be a reliable, valid, and feasible test to measure functional capacity in patients. Inter-tester variability was addressed as all testing was done by the principle researcher under the same reciprocated conditions as recommended by Jakobsen *et al*., (2010). Existing literature on the method of test performance emphasised that the participants start in the seated

position and sit in the middle of a 50cm high chair with their arms crossed against the chest, feet flat on the floor and back straight up against the backrest of the chair. The participant was then instructed to sit and stand - a stop watch was used to count down 60 seconds and the number of completed repetitions were recorded at all four time intervals (T1-T4) (Huber *et al.*, 2016).

3.4.7 Data analysis

Statistical analysis was performed using the Statistica v13.3 programme (TIBCO Software., 2017). After assessing the normal distribution of the data using the Shapiro-Wilks test, descriptive data were presented as mean ± standard deviation (SD). The difference between baseline and post-study period analysis of co-variance (ANCOVA) is presented as effect sizes (Cohen's d) and the differences between study groups were determined using ANOVA (analysis of variance). Paired t-tests were used to measure differences between baseline and post intervention data for all variables.

Independent t-tests were performed to determine if the intervention groups differed in basic participant characteristics. Repeated measures ANOVA tests with between-subjects' effects (exercise vs LLLT or exercise vs combined LLLT-exercise group) and within-groups effects (T2, T3, T4) were performed to indicate the difference in measurements from baseline. Significance was accepted at $p<0.05$.

3.5 Intervention Programme

3.5.1 Low level laser therapy

Participants in the LLLT group were exposed to three different arrays over a period of 12 sessions, with each session progressing from 35 minutes to 45 minutes (Kahn, 2008). These sessions were scheduled as two to three sessions a week. A circumferential application method was employed by a qualified physiotherapist who assisted with data collection. Three placements with medial and lateral application overlapping at the patella surface were used. The participant's knee was treated in a 110°-120°extension for optimal penetration of light from the light emitting diodes (LED). The probe was used to treat circumferentially around the patella. (Appendix 6 is a detailed LLLT protocol followed during the study.)

TABLE 5: LOW LEVEL LASER THERAPY DOSAGE

TREATMENT HEAD	FREQUENCY	DUTY CYCLE	DURATION
SLD -R 500	Constant wave	N/A	3 placements I. Circumferential (6mins) II. Medial (6mins) III. Lateral (6mins)
SLD-I 1000	50 Hz	50 -90	3 placements I. Circumferential (6mins) II. Medial (6mins) III. Lateral (6mins)
LD – I 200 (probe)	Constant wave	N/A	6mins

SLD: Super luminous diodes; LD: Laser diode; N/A: not applicable

3.5.2 Exercise intervention

The exercise programme was conducted three times per week and included 12 sessions for the LLLT combined with exercise group and the exercise alone group. The protocol for these sessions was based on data from a systematic review on KOA exercise rehabilitation (Fransen *et al.*, 2015). The exercises included four different types of exercise: flexibility, stability, strength and endurance (Appendix 7). The exercise programme was designed to maintain and improve knee functionality through improved muscular strength, range of motion and locomotor function of the knee joint. For this reason, the programme was developed to be self-paced and become progressively more challenging based on the principal investigator's extensive clinical experience.

3.6 Ethical Considerations

Approval for this study [Appendix 1] was granted by the Human Research Ethics Committee (Medical) at the University of the Witwatersrand before commencing with the study (ethics certificate number: M1611112). Participation in the study was voluntary and all participants were made aware of this fact before agreeing to participate. All participants signed an informed consent form (Appendix 8). The researcher was available to answer any questions/queries prior to signing the consent form. Each participant received a document (Appendix 9) prior to signing the informed consent form, explaining all the above, as well as details pertaining to the study and participation requirements. Participants were encouraged to ask questions during the data collection process or voice any concerns. Furthermore, all participants were

informed that they could withdraw from the study at any time, without prejudice. All results were treated confidentially during the entire research process. All data sheets were coded, participant names were removed, and all data sheets are stored in a locked filing cabinet located at the PI's clinical practice.

3.7 Summary

This methodology chapter has addressed the three themes that emerged from the research study: firstly, the prevalence of KOA in RSA, secondly, the treatment paradigm study to identify practitioner KOA management protocols, and thirdly, the intervention study on the use of exercise and LLLT in isolation or as a co-modality in the management of KOA. In summary, data analysis and synthesis provided preliminary evidence to add to the body of knowledge by suggesting a comparable nationally and internationally KOA significance rate, treatment paradigm data, and conclusion suggesting the effective use of exercise and LLLT as a co-modality in the management of the KOA patient.

PART 2

CHAPTER 4

4. RESULTS

The results in this chapter are discussed in two different sections - section A: findings of the prevalence treatment paradigm studies and section B: results as reported by the intervention study publication.

SECTION A

4.1 Prevalence Study

The study utilised a descriptive survey method with convenience sampling to investigate the prevalence of KOA in South Africa and the current management thereof.

All approached medical aid schemes were asked to provide data over a fiscal year under the nineteen ICD-10 codes (Appendix 2) earmarked for the use in KOA claims. The data were synthesised for three responsive private medical aid scheme using descriptive statistics; however, due to the non-responsiveness or inability of the other scheme/s to provide the study with the relevant data, prevalence could not be confidently determined.

TABLE 6: DESCRIPTIVE DATA: DEEMED KOA PREVALENCE

	TOTAL NUMBER OF CLAIMS (>45YRS)	%OF KOA CLAIMS
Scheme A	849757	17.4700
Scheme B	637317	27.9700

Scheme C	509854	38.5200
Total	1996928	83.9600
Mean ± SD	998464 ± 140202.88	41.9800 ± 8.59
Min	509854	17
Max	849757	38.5200

KOA = knee osteoarthritis

4.4 Treatment Paradigm Study

4.3.1 Practice delineation

The principal investigator sent out 742 questionnaires, with a 56% response rate after a six month continuous follow up process. The practitioner distribution after receiving four hundred and thirteen (n=413) responses was as follows:

i. General practitioners (n=110 / 26.63%) included all practitioners practicing general medicine
ii. The specialist practitioner designation (n= 117 / 28.32%), i.e. orthopaedic surgeon, general surgeons, neurologist and rheumatologist
iii. The allied professional practice designation (n=158 / 38.25%), i.e., Biokineticists, physiotherapists, occupational therapists, and chiropractors
iv. Natural healing practitioners (n=28 / 6.77%), i.e. homeopaths and naturopaths.

4.3.2 Percent of total patients observed with diagnosed KOA

Practitioners were asked to provide the percentage of patients consulting with KOA as the primary consulting diagnosis. The mean percentage of KOA patients seen at a practice was identified as 53.3% ±17.42% on a monthly basis. The incidence of

bilateral KOA was equally as high (65.4%±18.73%). Table 7 indicates the percentage of KOA and bilateral KOA patients seen according to practice delineation.

TABLE 7: KOA STATISTICS: DESCRIPTIVE DATA

		Mean (%)	SD
All (n=413)	%_KOA	53.31	±17.42
	%_BI_KOA	65.44	±18.73
General practitioner (n=110)	%_KOA	52.75	±12.1
	%_BI_KOA	66.23	±27.7
Specialist practitioner (n=117)	%_KOA	57.09	±11.49
	%_BI_KOA	64.98	±13.24
Allied practitioner (n=158)	%_KOA	50.6	±23.91
	%_BI_KOA	65.94	±15.74
Natural healing practitioner (n=28)	%_KOA	55	±6.38
	%_BI_KOA	61.43	±6.36

KOA: Knee osteoarthritis; BI_KOA: Bilateral knee osteoarthritis: SD: Standard deviation

4.3.3 Treatment modes

Study participants were asked to identify the most commonly suggested treatment mode for the management of KOA. The data received were computed using frequency modes. Figure 6 is a diagrammatic representation of the suggested management protocols for the KOA patient. The most frequently suggested treatment

mode for KOA is pharmacological, followed by exercise as an intervention with the smallest percentage of practitioners recommending LLLT.

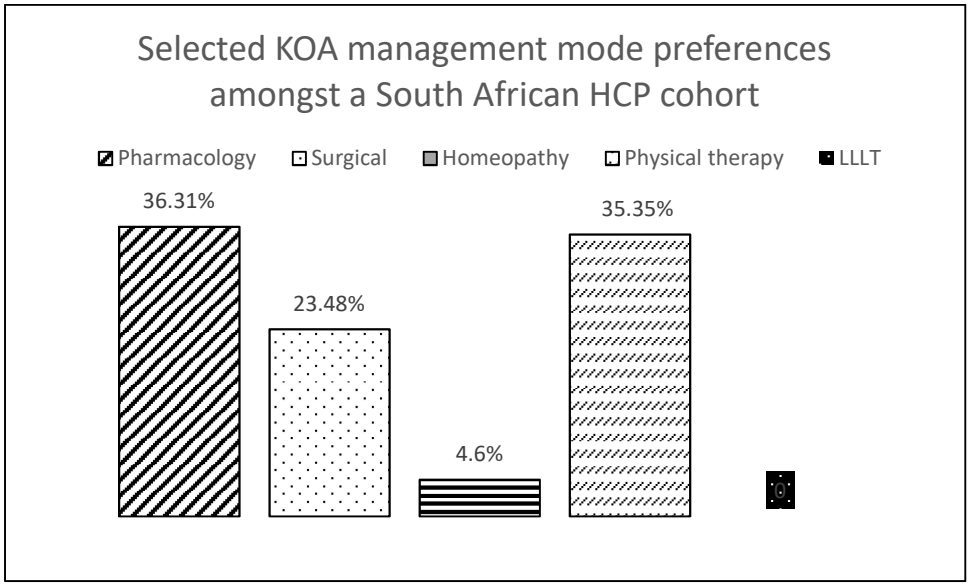


FIGURE 6: SELECTED KOA MANAGEMENT MODE PREFERENCES AMONGST A SOUTH AFRICAN HEALTHCARE PRACTITIONER COHORT

4.3.4 Deemed treatment mode effectiveness

When asked whether they thought the various treatment modes were effective in the treatment of KOA, 92% of practitioners reported exercise as an effective mode of treatment for KOA. Seventy three percent of all respondents felt that pharmacological intervention is an effective treatment mode for patients with KOA. Surgical intervention, homeopathic treatments and LLLT followed respectively.

Exercise therapy was the treatment mode of choice for allied practitioners. This practice designation listed exercise therapy as the most effective treatment for patients

with KOA. However, 41% of allied practitioners and 39% of general practitioners responded with a “no comment” to the deemed efficacy of LLLT in the management of KOA.

TABLE 8: DEEMED EFFICACY OF FIVE KOA MANAGEMENT PROTOCOLS

	Practice type	Effective	Non-effective (%)	No comment (%)	χ2 / (P value)
Deemed compliance of **pharmaceutical** interventions	All (n=413)	74%	26%	0%	17.3 0.0
	GP (n=110)	77%	23%	0%	
	SP (n=117)	81%	19%	0%	
	AP (n=158)	63%	37%	0%	
	NHP (n=28)	89%	11%	0%	
Deemed compliance of **surgical** interventions	All (n=413)	30%	69%	0%	7.8 -0.1
	GP (n=110)	35%	65%	0%	
	SP (n=117)	70%	30%	0%	
	AP (n=158)	24%	76%	0%	
	NHP (n=28)	46%	54%	0%	
Deemed compliance of **homeopathic**	All (n=413)	22%	52%	26%	11.2 -0.1
	GP (n=110)	27%	51%	22%	
	SP (n=117)	25%	44%	31%	
	AP (n=158)	20%	56%	24%	
	NHP (n=28)	4%	64%	32%	

interventions					
Deemed compliance of **exercise therapy**	All (n=413)	93%	4%	3%	21.1 0.0
	GP (n=110)	83%	10%	7%	
	SP (n=117)	97%	1%	3%	
	AP (n=158)	97%	2%	1%	
	NHP (n=28)	96%	0%	4%	
Deemed compliance of **LLLT**	All (n=413)	25%	42%	33%	49.3 0.0
	GP (n=110)	43%	36%	21%	
	SP (n=117)	7%	56%	36%	
	AP (n=158)	24%	34%	42%	
	NHP (n=28)	29%	54%	18%	

χ^2: Pearson's Chi Squared valued; *p*: P value; GP: general practitioner; SP: specialist practitioner; AP: allied practitioner; NHP: natural healing practitioner; LLLT: Low level laser therapy.

All four practice types (general, specialist, allied and natural healing practitioners) viewed exercise as an effective treatment mode for the management of the KOA patient. Regarding pharmaceutical therapy, there was not a marked difference amongst the data collected from general practitioners, specialists and homeopathic practitioners regarding the efficacy of it as a treatment mode. However, allied practitioners viewed pharmacological treatment efficacy with decreased vigour when compared to the other three designations. LLLT was not recommended as a general treatment mode for patients with KOA; however, when asked the effectiveness of LLLT

as a treatment mode for this patient population, all four practice types were in agreement in its positive effect on the condition, with general and homeopathic practitioners exhibiting the highest levels of confidence. Seventy five percent of all practitioners responded to the question of LLLT and its effectiveness for the treatment of KOA with “no comment”. This result lends to the exploration and practitioner enlightenment regarding the physiology of the use of LLLT for the treatment of KOA.

4.3.5 Deemed Compliance of proposed treatment modes

When asked about perceived patient compliance with regard to the various treatment modes, 61.9% of the responding practitioners felt that patients were most compliant with physical exercise therapy sessions. This is a very encouraging statistic, as continued exercise and wellness promotion leads to an improvement in ADL’s. Practitioners viewed pharmacological compliance after exercise compliance, but with a similar score of 60%. Forty three point nine percent of all responding practitioners responded to the compliance rate with regard to LLLT as “no comment” – meaning that they did not have enough information available to ascertain the compliance of this treatment mode.

TABLE 9: DEEMED COMPLIANCE OF FIVE KOA MANAGEMENT PROTOCOLS

	Practice type	Compliant	Non-compliant (%)	No comment (%)	χ2 / (P value)
Deemed compliance	All (n=413)	60%	40%	1%	58.1
	GP (n=110)	75%	25%	1%	0.0

of **pharmaceutical** interventions	SP (n=117)	68%	33%	0%	
	AP (n=158)	38%	61%	1%	
	NHP (n=28)	93%	7%	0%	
Deemed compliance of **surgical** interventions	All (n=413)	23%	76%	1%	5.3 -0.5
	GP (n=110)	23%	76%	1%	
	SP (n=117)	21%	76%	3%	
	AP (n=158)	24%	75%	1%	
	NHP (n=28)	29%	71%	0%	
Deemed compliance of **homeopathic** interventions	All (n=413)	20%	43%	37%	9.7 -0.1
	GP (n=110)	23%	36%	41%	
	SP (n=117)	25%	39%	36%	
	AP (n=158)	18%	47%	35%	
	NHP (n=28)	4%	57%	39%	
Deemed compliance of **exercise therapy**	All (n=413)	62%	32%	6%	83.9 0.0
	GP (n=110)	41%	37%	22%	
	SP (n=117)	62%	37%	1%	
	AP (n=158)	70%	30%	0%	
	NHP (n=28)	96%	0%	4%	
	All (n=413)	19%	37%	44%	63.9
	GP (n=110)	5%	45%	50%	0.0

Deemed compliance of **LLLT**	SP (n=117)	38%	33%	29%	
	AP (n=158)	13%	31%	56%	
	NHP (n=28)	36%	50%	14%	

Chi (χ^2): Pearson's Chi Squared valued; *p*: P value; GP: general practitioner; SP: specialist practitioner; AP: allied practitioner; NHP: natural healing practitioner; LLLT: Low level laser therapy.

SECTION B

4.3 Intervention Study

4.3.1 Subject characteristics

A total of 126 participants were sourced for the study from referring medical and allied practitioners within the Gauteng province, after the initial study call was sent out. Six potential patients did not meet the inclusion criteria, as three were unable to complete the physical functionality test, one potential participant did not agree to participate in the study due to randomisation of intervention protocol, and two potential participants were unable to attend sessions due to logistical constraints. The 120 participants sampled for the study were randomly allocated to the three intervention groups (40 participants each). The final tally at study culmination was exercise group (n= 39), LLLT group (n=40) and the combined LLLT-exercise group (n=32); 85 of them were women (76.57%) and 26 were men (23.42%), with an average age of 61.8yrs and SD of 5 yrs. There was no significant difference in the baseline characteristics of the 111 patients randomised in the study (Table 1) making them suitable for comparison.

TABLE 10: INTERVENTION STUDY: PARTICIPANT DEMOGRAPHIC

	All (n=111)	Exercise (n=39)	LLLT (n=40)	Combined exercise-LLLT (n=32)
Gender (♀♂)	86♀ 25♂	26♀ 14♂	32♀ 7♂	28♀ 4♂
Age (yrs.)	61.8 ± 5.6	62.2 ± 6.0	62.0 ± 5.1	61.1 ± 5.6

Weight (kg)	80.7 ± 16.6	77.8 ± 13.4	81.9 ± 20.1	82.7 ± 14.7
Height (cm)	160.3 ± 10.1	162.1 ± 6.7	157.5 ± 13.3	161.4 ± 8.0
BMI (kg/cm^2)	32.5 ± 18.8	29.6 ± 4.6	36.1 ± 5.3	31.6 ± 4.4

Data presented as mean ± SD

Abbreviations: LLLT=low level laser therapy; BMI = Body mass index, yrs. = years, kg = kilograms, cm = centimetre Index

Symbols: ♀ = female, ♂ = male

4.3.2 Baseline characteristics

TABLE 11: BASELINE AND POST INTERVENTION CHARACTERISTICS OF THE SAMPLE

	Exercise (n=39)		**LLLT (n=40)**		**Combined exercise-LLLT (n=32)**	
	Baseline	**Post-intervention**	**Baseline**	**Post-intervention**	**Baseline**	**Post-intervention**
Knee circumference (Proximal Patella) (cm)	41.4 ± 6.1	38.0 ± 6.1*	41.3 ± 6.1	40.0 ± 6.1*	43.5 ± 7.3	41.1 ± 7.4*
Knee circumfer	36.6 ±	38.9 ± 4.5*	38.5 ±	40.3 ±	40.0 ±	39.2 ± 3.9*

ence (mid patella) (cm)	5.1		4.8	4.5*	4.6	
Knee circumference (Distal patella) (cm)	37.4 ± 4.3	36.6 ± 4.2*	36.3 ± 4.7*	37.9 ± 3.1*	37.7 ± 4.6	37.5 ± 4.0*
WOMAC	56.6 ± 10.1	60.8 ± 9.8*	59.1 ± 10.2	61.5 ± 11.3*	56 ± 10.8	65.6 ± 9.9*
ROM-Extension (º)	2.1 ± 2.8	1.1 ± 1.9*	1.6 ± 2.5	1.4 ± 2.1*	1.4 ± 2.5	0.8 ± 1.6*
ROM-Flexion (º)	99.5 ± 14.6	102.3 ± 16.9	96 ± 17.4	103.7 ± 11*	95.2 ± 19.1	108.3 ± 11.9*
Sit-to-stand (reps)	17 ± 2.5	19.7 ± 3.5*	17.1 ± 2.9	19.6 ± 3.2*	17.4 ± 3.5	21.3 ± 4.1*

Data presented as mean ± SD

Abbreviations: LLLT=low level laser therapy; WOMAC =Western Ontario and McMaster Universities Arthritis Index, ROM = range of motion, º=degrees, reps = completed repetitions

Symbols: * p<0.05 vs baseline values

TABLE 12: KOA OUTCOMES (T2, T3, T4) – ADJUSTED MEAN CHANGES AND EFFECT SIZES BY INTERVENTION GROUP

	Exercise (n=39)			LLLT (n=40)			Combined exercise - LLLT (n=32)		
Variable	**T2**	**T3**	**T4**	**T2**	**T3**	**T4**	**T2**	**T3**	**T4**
Proximal Patella (cm)	40.0 ± 6.1*	38.3 ± 6.4*	38.0 ± 6.1*	38.0 ± 6.1*†	36.7 ± 6.1*†	35.2 ± 6.2*†	41.1 ± 7.4*	39.6 ± 6.7*†	38.3 ± 6.7*
	0.2 (-0.2:0.7)	***0.5 (-0.0:0.9)***	***0.6 (0.1:1.0)***	***0.3 (-0.1:0.8)***	***0.3 (-0.2:0.7)***	***0.4 (0.0:0.9)***	***0.2 (-0.6:0.3)***	***0.2 (-0.7:0.3)***	***0.1 (-0.5:0.4)***
Mid patella (cm)	40.3 ± 1.4	38.6 ± 4.5*	37.4 ± 4.5*	38.9 ± 4.5†	36.8 ± 4.2*†	36.0 ± 4.2*	39.2 ± 3.9†	37.0 ± 3.1*†	36.5 ± 3.7*†
	0.1 (-0.6:0.3)	***0.4 (-0.9:0.0)***	***0.2 (-0.6:0.3)***	***0.3 (-0.1:0.7)***	***0.4 (0.0:0.9)***	***0.3 (-0.1:0.8)***	***0.2 (-0.2:0.7)***	***0.4 (0.0:0.9)***	***0.2 (-0.2:0.7)***
Distal patella (cm)	37.9 ± 3.8*	38.0 ± 4.4	37.4 ± 3.6*	36.6 ± 4.2†	36.4 ± 4.2†	36.0 ± 4.2†	37.5 ± 4.0	37.3 ± 4.0	36.5 ± 3.7*†
	0.1 (-0.6:0.3)	***0.1 (-06:0.3)***	*0.0 (-0.5:0.4)*	***0.3 (-0.1:0.8)***	***0.4 (-0.1:0.8)***	***0.4 (-0.1:0.8)***	***0.1 (-0.4:0.6)***	***0.2 (-0.3:0.3)***	***0.3 (-0.2:0.7)***
	61.5 ± 11.3*	65.3 ± 13.1*	70.5 ± 11.8*	70.8 ± 9.8*†	76.9 ± 9.2*†	80.7 ± 8.5*†	65.6 ± 9.9*†	72.0 ± 8.7*†	78.0 ± 8.5*†

WOMAC	***0.5 (0.9:0.0)***	***0.7 (-1.2:0.3)***	***1.3 (-1.7:0.8)***	***0.9 (-1.3:-0.4)***	***1.0 (-1.5:0.6)***	***1.0 (-1.4:-0.5)***	***0.4 (-0.8:0.1)***	***0.6 (-1.1:-0.1)***	***0.7 (-1.2:-0.2)***
ROM Extension (º)	1.4 ± 2.1*	0.7 ± 1.5*	0.3 ± 0.9*	1.3 ± 1.9*	0.6 ± 1.3*	0.2 ± 0.6*	0.8 ± 1.6*†	0.4 ± 1.0*†	0.9 ± 0.4*†
	0.3 (-0.1:0.8)	***0.6 (0.2:1.1)***	***0.9 (0.4:1.3)***	***0.1 (-0.4:0.5)***	***0.1 (-0.3:0.5)***	*0 (-0.4: 0.4)*	***0.3 (-0.2:0.8)***	***0.3 (-0.2:0.7)***	*0 (-0.5: 0.5)*
ROM Flexion (º)	103.7 ± 13.4*	108.1 ± 12.4*	111.4 ± 11.5*	102.3 ± 16.9*	107.4 ± 14.9*	109.5 ± 13.2*	108.3 ± 11.9*†	112.3 ± 11.3*†	115.2 ± 10.3*†
	0.3 (-0.7:0.2)	***0.6 (-1.1:-0.2)***	***0.9 (-1.4:0.4)***	***0.1 (-0.4:0.5)***	***0.1 (-0.4:0.5)***	***0.2 (-0.3:0.6)***	***0.4 (-0.8:0.1)***	***0.4 (-0.8:0.1)***	***0.3 (-0.8:0.1)***
Sit-to-stand (reps)	19.5 ± 3.0*	23 ± 4.5*	26 ± 3.5*	19.7 ± 3.5*	25.5 ± 3.0*†	25.5 ± 4.0*	21.2 ± 4.0*†	25.5 ± 3.0*†	30.0 ± 3.0*†
	0.9 (-1.4:-0.4)	***1.6 (2.1:-1.1)***	***0.3 (-3.6:-2.3)***	***0.1 (-0.5:0.4)***	***0.7 (-1.1:-0.2)***	***0.1 (-0.3:0.6)***	***0.5 (-0.9:0.0)***	***0.7 (-1.1:-0.2)***	***1.2 (-1.7:-0.7)***

Data presented as mean ± SD with effect sizes (95% CIs)

Abbreviations: KOA=knee osteoarthritis; LLLT=low level laser therapy; T2=post intervention; T3=1 month post intervention; T4=3 months post intervention; reps = completed repetitions

Symbols: *italics* = effect size (95% CIs); **bold**=effect size >0.02; *p<0.05 (T1 vs T2, T1vs T3, T1 vs T4) using independent tests; †p<0.05 exercise vs LLLT, and exercise vs combined exercise-LLLT

4.3.5 Baseline (T1) to1 month post intervention (T3)

One month post intervention data were recorded for all three intervention groups across all variables (Table 12). Statistical significance was highlighted for WOMAC pain scale and physical functionality (p=0.0001) with participants undergoing LLLT in isolation or combination to exercise. These participants experienced an eight point's greater decrease in pain scale scores and 2 repetitions increased physical functionality

test scores. Small effect size (d=>0.2) is seen at 1-month post intervention for knee circumference values, when using exercise combination with LLLT or using LLLT in isolation. There is large and medium effect size (d=>0.5) in values for WOMAC pain scales with an average improvement of >7.34 when using LLLT as a treatment in isolation or as a co-modality to exercise. The data as presented by table 12 provided convincing evidence for the use of LLLT as a co-modality to exercise (d=>0.8) rather than utilising it in isolation (d=>05).

4.3.5 Baseline (T1) to 3 months post 12 session intervention (T4)

Long term intervention efficacy was calculated 3 months post intervention (Table 12). There were differences in all three groups with the combined LLLT-exercise group (p=0.0001) showing an improvement of 12 repetitions 3-months post intervention compared to an improvement of 8 and 9 repetitions for the LLLT or exercise only groups respectively. The data provide convincing evidence on the long term efficacy of using LLLT in isolation or as a co-modality to exercise with variables such as ROM and knee circumference exhibiting statistical significance ($p<0.05$) and small effect sizes ($d >0.2$). Overall this research project supports the validity and efficacy of LLLT in isolation or co-modality to exercise with large effect sized ($d>0.8$) for pain scores and physical functionality scores.

4.4 Knee Osteoarthritis Variable Outcomes

4.4.1 Knee circumference

Knee circumferences at baseline were significantly higher in the LLLT and combined groups versus the exercise group for proximal, mid- and distal patella circumferences ($p<0.05$) (Table 12). At 12-week follow-up knee circumference decreased significantly

in all groups ($p<0.05$), and this effect was highest in the LLLT group compared to the combined LLLT-exercise group and exercise groups (Fig.4.1).

4.4.2 WOMAC pain scale

Table 12 shows that all groups experienced improvements in the WOMAC pain scale, but that this was most noticeable in the exercise group ($p<0.05$). Values at baseline were comparative across all three intervention groups. At post intervention data collection (T2) the LLLT group achieved >5points greater improvement versus the exercise or combined LLLT-exercise group. However, the exercise vs LLLT had significantly greater effect sizes at T3 and T4 compared to the exercise vs combination group.

The decrease in knee circumference values and improvements in the WOMAC pain and functionality scores indicate structural enhancement in the joint due to a decrease in joint effusion evident by the decrease in knee circumference scores and an improvement in WOMAC pain and functionality score, as supported by authors; Alfredo *et al*., (2011); Fukuda *et al.*, (2015) and Alfredo *et al.*, (2018). Minimal Clinical Important Difference (MCID) for the WOMAC scales indicated the smallest change in treatment outcome that would indicate a change in the patient's management (Hedayat, Wang and Xu, 2015). Improvements between 11 and 12.9 points in a period of 2-6 month post intervention establishes minimal clinical important difference (MCID) when using the WOMAC as an evaluation tool (Angst, Aeschlimann and Stucki, 2002; Williams *et al*., 2012). The study showed greater than 11 point improvement (calculated mean difference between baseline and post intervention testing) in both groups exposed to LLLT at T3 and T4.

4.4.3 Knee ROM

Knee extension was significantly lower in the combined LLLT-exercise group and LLLT groups compared with the exercise group at baseline (Table 11). Only the combination group experienced significant improvements following the intervention (Figure 7). Baseline knee flexion was higher in exercise group compared with the LLLT and combined LLLT-exercise group ($p<0.005$); however, the effect of the intervention was only significant in the combination group (Figure 7).

4.4.4 Sit-to-stand

Baseline values for physical functionality assessments were similar across all three intervention groups. Figure 7 demonstrates that the combined LLLT-exercise group had greater improvements in sit-to-stand repetitions post-intervention, and this effect was evident 1-month and 3-months post intervention.

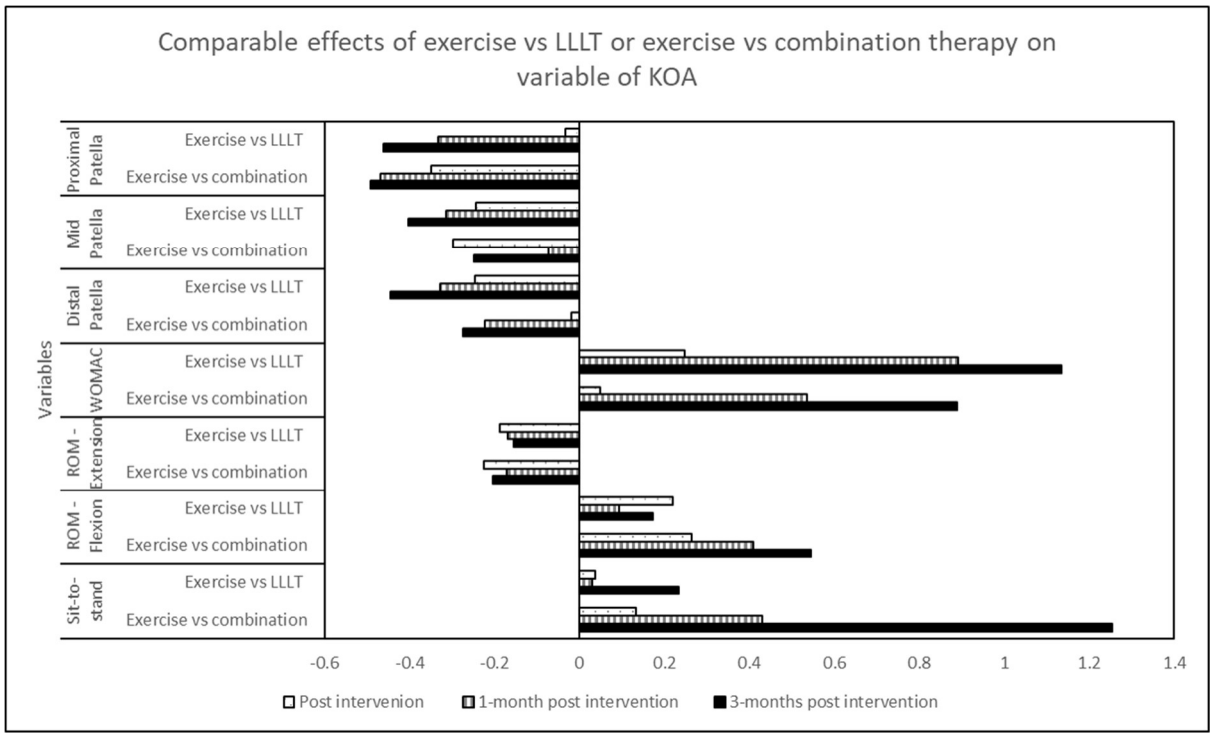


FIGURE 7: COMPARABLE EFFECTS OF EXERCISE VS LLLT OR EXERCISE VS COMBINATION THERAPY ON VARIABLES OF KOA

4.5 Intervention study discussion

The study aimed to evaluate the effects of utilising LLLT in combination with exercise in comparison to using exercise or LLLT in isolation for the conservative management of KOA. Varying effects were observed in all three groups for the key outcomes although the combined LLLT-exercise group demonstrated improved efficacy for outcome measures of knee circumference, WOMAC pain scale, knee ROM-flexion and a 1-minuted timed sit-to-stand test. The results documented during this intervention study have been supported by publications from Zhang *et al.*, (2009) and Hawkeswood and Reebye, (2010) iterating that modalities such as exercise and LLLT allow for the decrease of inflammation at the joint site, improvement in patient ROM, functionality and decreased pain.

4.5.1 Knee circumference

There was a significant reduction in knee circumference readings across all three groups during the current study; however, the LLLT group exhibited the greatest decrease across the intervention period. The combinative group, showed a greater decrease after 12 sessions as compared to the exercise group, which exhibited a lesser decrease, leading this study to the conclusion that, while LLLT alone decreased knee circumference, adding LLLT to exercise further enhances the beneficial effects. LLLT has been documented by Bjordal, Lopes-Martins and Iversen, (2006); Alfredo *et al.*, (2018) and Castaneda *et al*., (2012) to produce anti-inflammatory properties upon application due to osteoblastic and fibroblastic proliferation, collagen synthesis and micro vascularisation. The results obtained during this study are comparable to data reported by Alghadir *et al.*, (2014); Soleimanpour *et al.*, (2014); Alfredo *et al.*, (2018) and de Matos Brunelli Braghin *et al.*, (2018) which showed a decrease in knee circumference measures.

4.5.2 WOMAC pain scale

In the current study, the within-group analysis showed that KOA symptoms had significantly improved across all three intervention groups ($p<0.05$) with LLLT group exhibiting superiority at short term pain relief but the combined LLLT-exercise group showed far superior results at 3-month post intervention study. This implies that there is a residual positive effect of the treatment until three months post intervention even though the active treatment had stopped three months prior, with the implication that structured exercise prescription further aids results in the KOA patient. The exercise

group showed decreased in WOMAC scores, although the effect was much less pronounced. The improvement in the exercise group remained small throughout the study.

Knee osteoarthritis patients often feel that this disorder is associated with physical inactivity and age therefore inevitable, and not much can be done to modify its evolution, that treatments are of little help, and that medical and allied practitioners have not much knowledge on the various modalities available (Basaran *et al*., 2010). However, Bennell, Dobson and Hinman, (2014) have alluded to the determining benefits of adherence and compliance for sustained long term effects. Patients are not often compliant with exercise as a modality due to financial and logistical constraints; they often state that exercise is too difficult and immediate decrease in pain is not felt (Pearson *et al*., 2016). Therefore, adding a modality like LLLT to address pain as seen by the data collected from the WOMAC pain scale would be beneficial and aid in adherence and earlier discharge from supervised rehabilitation settings.

4.5.3 Knee range of motion (flexion and extension)

Knee range of motion (ROM), as an assessment tool for the current study, showed a significant improvement at all assessment periods for participants in all three groups, the improvement in the exercise group was the highest for knee ROM – extension, whereas the combined LLLT-exercise group mode showed the best and steadiest improvement for knee ROM – flexion. The short- and long-term improvements in the

ROM can be attributed to the combinative treatment mode not discounting the positive effects of either intervention mode individually applied.

Consequently, an interesting finding emerging from the data collected during this study, was that at baseline, patients exhibited a higher average knee ROM when compared to other similar studies (Gur *et al.*, 2003; Fukuda *et al.*, 2011; Alfredo *et al.*, 2018). Therefore, in the current study, less significant results were seen when comparing intergroup differences. This collected data is supported by a previous publication by Szabo *et al*., (2000), who found that Muslim Arabs with KOA have an average ROM of 139.5°, which is higher compared to the 102.8° non-Muslim Arab counterparts. This is attributed to the lifestyle practised by Muslim societies causing deep flexion of the knee joint during the five daily prayers. This deduction is key due to the percentage of Muslim participants in the study.

4.5.4 Physical functionality

Baseline values for physical functionality assessments were similar across all three intervention groups. The combined LLLT-exercise group had greater improvements in sit-to-stand repetitions post-intervention, and this effect was evident across all three data collection time points. It has been documented by Strong, (2002) and Watson, (2000) and as seen in clinical practice that KOA patients have a significant reduction in their physical activity levels as a result of their tendency to avoid pain. This leads to decrease cardiovascular fitness, altered muscular strength and endurance associated with the joint and decreased levels of ROM. These limitations are directly linked to the patients' ability for self-care, resulting in an impaired QOL. Functional

improvements were observed by the increased number of timed sit-to-stand repetitions and improvements in knee flexion ROM. The findings from this study set a discussion point for both structural and functional management traits in KOA.

Exercise (Iwamoto, 2011; Conroy *et al*., 2012) and other modalities such as LLLT (Fukuda *et al.*, 2011; Alghadir *et al.*, 2014; Tomazoni *et al.*, 2017; Alfredo *et al.*, 2018) playing to addressing these concerns and are key in the treatment of KOA. This research study suggests that analgesia associated with LLLT results in the anti-inflammatory properties on the articular capsule as suggested by the World Association of Laser Therapy (WALT), with similar results being produced, resulting in both pain relief and a decrease in knee circumference values (Alfredo *et* al., 2011; Fukuda *et al.*, 2011; Alfredo *et al.*, 2018). The current study appears to support these notions as data collected show that using exercise in isolation or as a co-modality to exercise has a reduction in pain symptoms ($p<0.05$), reduction in inflammation ($p<0.05$) around the knee joint, improvement in ROM ($p<0.05$) and an improvement functionality scores ($p<0.05$).

CHAPTER 5

5. DISCUSSION

5.1 Introduction

This PhD thesis set out to investigate the prevalence of KOA in South Africa using data from South African medical schemes, the efficacy and compliance of management choices for patients with KOA, and the use of exercise and LLLT for the management of KOA.

5.2 Summary of the main thesis findings

The objectives of this thesis and related findings are three fold:

(i) To investigate the prevalence of KOA in South Africa – the prevalence rates obtained from medical scheme providers within South Africa indicate a 17.4 – 38.5% prevalence in males and females, >45yrs seeking medical attention over a single fiscal year. These findings are not without its limitations due to the cohort of study participants not being inclusive of the South African population.

(ii) The current management of KOA in South Africa indicated that amongst healthcare practitioners, pharmacological management followed by physical exercise therapy were observed to be the common treatment options for KOA. LLLT was not noted as a management option. Healthcare practitioners reported physical exercise therapy as effective for managing KOA while reporting that pharmacotherapy may not be the most effective management tool for patients with KOA. Furthermore, healthcare practitioners were not aware of the effectiveness of LLLT as a treatment

modality. Lastly, the cohort of tested healthcare practitioners perceived that patients diagnosed with KOA were compliant with physical exercise therapy for 61% of the rehabilitation programme, while deemed compliance regarding LLLT as a treatment option could not be ascertained.

(iii) The effects of exercise and LLLT on the functional components of KOA within the southern areas of Johannesburg, South Africa reported that knee circumference values decreased the greatest in the LLLT compared to that of the combined LLLT-exercise group or exercise group. The LLLT had significantly greater effect sizes at all three post intervention compared to the group not receiving any LLLT intervention for WOMAC pain scale values. Knee ROM, flexion and extension values improved significantly across all three intervention groups; however, the effect of the intervention was significant in the combined LLLT-exercise group. Physical functionality scores as measured by the timed-sit-to-stand test showed a greater improvement in the combined LLLT-exercise group at all three post intervention data collection points.

5.3 Emerging Themes from the PhD

Three main themes were observed in this PhD study. These include the difficulties with determining the presence of KOA, lack of familiarity among medical and allied practitioners on the use of alternative therapies in the management of KOA and using novel approaches to the management of patients with KOA.

5.3.1 Difficulty estimating KOA prevalence

Pain and lowered functionality are common reasons for KOA patients consulting and subsequently claiming for consultations with clinicians. These claims are tracked and analysed through healthcare databases housed by medical aids. These databases assist medical aids with determining the economic burden of diseases, and subsequent healthcare costing. The findings of this PhD show that the estimated prevalence of KOA in South Africans is 38.5%, which is significantly lower than the estimate observed in other studies such as that of (Usenbo *et al.*, 2015). The data reported in this PhD study highlight two limitations, which uncovers the difficulty with estimating the presence of KOA.

These are:

(i) Methodological – The data were provided by the key medical aid providers in South Africa, but these data are potentially biased as they represent those covered by private healthcare companies and are not representative of the broader population. Only three of the five medical aid companies provided data on KOA, suggesting missing data. A large scale survey is therefore required for better knowledge on the epidemiology of KOA. Moreover, the South African Government Gazette has reported that only seventeen percent of all South Africans have access to private medical aid (Department of Health, 2018); therefore, data collected are is a misrepresentation of the KOA cohort.

(ii) Data reporting limitation – The ICD-10 coding system is beneficial for capturing disease specific data; however, our findings have shown that a number of possible

OA-related ICD-10 codes may be used for KOA management. This is another reason for not having a good understanding of the presence of KOA in South Africa. A more robust system is needed to capturing KOA-specific claims.

A study by Groenewald *et al*., (2005) observed that, South Africa has prioritised the collection of reliable cause-of-death statistics to inform health policy and efforts have been made to improve registration and data collection. Priority and resources are given to HIV and AIDS and infant, child and maternal health, and not to conditions such as KOA. Despite this, KOA is a form of OA that continues to increase the burden associated with non-communicable diseases-related mortality. In addition to being listed as the fastest increasing health condition, OA is a major cause of disability with reports showing an increase by 45% from 1990 to 2010 (Cross*et al.*, 2014; Woolf, 2015).

Data collected from this study could not be extrapolated to a broader South African cohort due to the study cohort being unrepresentative of the population, therefore the current thesis adds updated data on the prevalence of KOA to a limited body of evidence. This information is important for understanding the epidemiology of KOA in the country and can help practitioners with targeted management programmes for diagnosed patients.

5.3.2 Knowledge on selected non-surgical management strategies for KOA

This PhD study has reported that pharmacotherapy is the most frequently suggested and used treatment option for the patients diagnosed with KOA. This is an interesting

finding as the literature is not clear on the effects of pharmacotherapy in managing the disease. For example, studies have shown that this method of treatment does not completely address joint and patient functionality or disease modification (Chevalier and Henrotin, 2009). The goal of treatment for KOA is essentially to alleviate the symptoms and slow the progression of the disease (Joern *et al*., 2010; Fransen *et al.*, 2015). While the management of KOA ranges from general measures such as home remedies, to physiotherapy, orthopaedic aids, pharmacotherapy, regenerative medicine and finally surgery in order to control pain and improve function, our findings support the evidence that practitioners are not aware of adjunctive therapies to assist with patient care for KOA (Grol and Grimshaw, 2003; Alami *et al*., 2011). This thesis demonstrates the use of LLLT as a novel method of treating KOA in a non-invasive manner. In combination with traditional exercise therapy, LLLT was shown to address the structural and functional limitations related to the disease in the study sample.

Physical exercise therapy was observed as a common form of conservative management for KOA. The study sample (clinicians) were not aware of LLLT as a potential treatment modality. The findings of our study highlight the benefits of LLLT as a modality amongst KOA patients. One the key benefits for clinicians is the potential for lowering the duration of patient contact time, as was shown with this methodological approach. This research study therefore makes the cases for the urgent need for translation of evidence to practice, particularly as the burden KOA increases.

5.3.3 Novel approaches to the management of KOA

Technology is improving continually and has found a platform within therapeutic medicine, resulting in improved knowledge for patients and practitioners (Harari, 2017). A multi-disciplinary approach to managing patients with KOA is accepted as the most preferred (Campbell-Hall *et al*., 2010). In addition to the use of technology, there is a drive toward inter-professional patient care in chronic conditions such as KOA (Reeves *et al*., 2013). Working in a collaborative team of physical exercise therapists and laser therapist would result in an earlier discharge from supervised rehabilitative care (Halamka, 2018).

PART 3

CHAPTER 6

6. LIMITATIONS, RECOMMENDATIONS AND CONCLUSIONS

This chapter will discuss the conclusions relating to the current study, as well as the limitations, implications of the findings and recommendations for future research.

6.1 Limitations

The data on the prevalence of KOA and the study population recruited for the RCT were from a select cohort, i.e. data for the prevalence study were from 60% of private medical aid schemes, and the sample for the RCT were recruited from a region with a predominant ethnic origin, and so the data may not fully represent the South African population. In addition, even though the list of ICD-10 codes supplied are in line with KOA diagnosis, the practitioners may have used non-specific codes for diagnosis, resulting in the difficulty to understand the epidemiology of KOA.

6.2 Theoretical Relevance and Implication of Findings

Non-communicable diseases such as OA and in particular KOA are increasing in both rural and urban areas (Usenbo *et al.*, 2015). This increase has led to an increased economic burden on global healthcare (Tollman *et al*., 2008), and consequent pressure on clinicians to continue managing NCDs proficiently. The thesis has shown that there is a misrepresentation of KOA from key South African medical aid databases. Furthermore, the study demonstrated that clinicians have a limited knowledge of the non-surgical management options for KOA. Our findings add to the limited evidence on the prevalence and management of KOA.

The findings support evidence from developed setting that LLLT, in isolation or combined with physical exercise, can result in reduced pain and inflammation around the knee joint, and improvements in ROM and patient functionality. Indeed, using LLLT with physical exercise was observed as the most beneficial to structural and functionality.

6.3 Recommendations

The research project highlighted several areas where further investigation is required:

- Research is required in identifying and documenting the prevalence of OA and joint specific OA in the wider South African population, taking into cognisance the limitations experienced during this research study.
- Further research is required in identifying the need of educating medical and allied practitioners on the use of LLLT for the management of OA and related disorders.
- As the current study is the first study to use quantitative methodology using the 3 stage LLLT implementation for KOA, it provides a model for future research. Further well-designed RCT's with longer term findings are required, to establish efficacy with regards to wavelength, duration, dosage and site of application.

6.4 Conclusions

This PhD aimed to determine the prevalence of KOA in the South African population. It was designed to retrieve data predominantly from the primary medical aid schemes in the country. The prevalence of the disease was observed to be lower than anticipated. This was possibly due to general ICD-10 codes for OA, rather than specific

codes for KOA being used by clinicians for claiming. Nevertheless, the data provided estimates incidence of KOA for the ‘covered’ South African population and suggest further investigation in the public healthcare setting.

The research undertaking aimed to determine the management options for KOA amongst clinicians. The findings show that pharmacotherapy is common, whilst demonstrating that clinicians view physical exercise therapy as effective. LLLT was not a known tool for the treatment of KOA. The study contributes to the body of knowledge suggesting that practitioner training, and potentially through workshops and dissemination of our findings are required to improve the knowledge and potential use of LLLT in the clinical setting.

This thesis set out to determine the efficacy of LLLT in the treatment of KOA. The data gathered during this study has shown that LLLT used in isolation or in combination with physical exercise is an effective management tool. The combined approach to management seems to be the best option for KOA patients, but this needs further investigation. In addition to the improved functionality observed in the study population, pain was lowered significantly, and particularly amongst the participants included in the combined exercise-LLLT group.

References:

1. Abate, M., Pulcini, D., Lorio, A.D. and Schiavone, C. (2010). Visco-supplementation with intra-articular hyaluronic acid for treatment of osteoarthritis in the elderly. Pharmaceutical Design; 16: 631-640.
2. Abrisham, S.M., Kermani-Alghoraishi, M., Ghahramani, R., Jabbari, L., Jomeh, H, and Zare, M. (2011). Additive effects of low-level laser therapy with exercise on subacromial syndrome: a randomised, double-blind, controlled trial. Clinical Rheumatology; 30: 1341-1346.
3. Adams, N., Poole, H. and Richardson, C. (2006). Psychological approaches to chronic pain management. Journal of Clinical Nursing; 15: 290-300.
4. Ageberg, E. and Roos, E. (2015). Neuromuscular exercise as treatment of degenerative knee disease. Exercise and Sport Sciences Reviews, 43(1):14-22.
5. Ageberg, E. and Roos, E. (2015). Neuromuscular exercise as treatment of degenerative knee disease. Exercise and Sport Sciences Reviews, 43(1):14-22.
6. Ahn, A.C., Colbert, A.P., Anderson, B.J., Martinsen, O.G., Hammerschlag, R., Cina, S. (2008). Electrical properties of acupuncture points and meridians: a systematic review. Bio electromagnetics; 29: 245-256.
7. Ahsin, S., Saleem, S., Bhatti, A.M., Iles, R.K. and Aslam, M. (2009). Clinical and endocrinological changes after electro-acupuncture treatment in patients with osteoarthritis of the knee. Pain; 147: 60-6.
8. Alami, S., Boutron, I., Desjeux, D., Hirschhorn, M., Meric, G., Rannou, F. (2011) Patients' and Practitioners' Views of Knee Osteoarthritis and Its

Management: A Qualitative Interview Study. Peer Reviewed Open Access Scientific Journal One, 6(5): e19634.

9. Alfredo, P., Bjordal, J., Dreyer, S., Meneses, S., Zaguetti, G., Ovanessian, V., Fukuda, T., Junior, W., Martins, R., Casarotto, R. and Marques, A. (2012). Efficacy of low level laser therapy associated with exercises in knee osteoarthritis: a randomized double-blind study. Clinical Rehabilitation, 26(6), pp.523-533.
10. Alfredo, P., Bjordal, J., Junior, W., Lopes-Martins, R., Stausholm, M., Casarotto, R., Marques, A. and Joensen, J. (2018). Long-term results of a randomized, controlled, double-blind study of low-level laser therapy before exercises in knee osteoarthritis: laser and exercises in knee osteoarthritis. Clinical Rehabilitation, 32(2), pp.173-178.
11. Alfredo, P.P., Bjordal, J.M., Dreyer, S.H., Meneses, S.R.F., Zaguetti, G., Ovanessian, V., Fukuda, T.Y., Junior, W.S., Martins, R.A.B.L., Casarotto, R.A. and Marques, A.P. (2011). Efficacy of low level laser therapy associated with exercises in knee osteoarthritis: A randomized double-blind study, Clinical Rehabilitation, 26(6), 523–533.
12. Alghadir, A., Omar, M., Al-Askar, A. and Al-Muteri, N. (2014). Effect of low-level laser therapy in patients with chronic knee osteoarthritis: a single-blinded randomized clinical study. Lasers in Medical Science, 29(2), pp.749-755.
13. AlGhamdi, K.M., Kumar, A., Moussa, N.A. (2011). Low-level laser therapy: a useful technique for enhancing the proliferation of various cultured cells. Lasers Medicine and Science; 27: 237-249.
14. Altman, R., Asch, E., Bloch, D., Bole, G., Borenstein, D., Brandt, K., Christy, W., Cooke, T., Greenwald, R., Hochberg, M., Howell, D., Kaplan, D.,

Koopman, W., Longley, S., Mankin, H., McShane, D., Medsger, T., Meenan, R., Mikkelsen, W., Moskowitz, R., Murphy, W., Rothschild, B., Segal, M., Sokoloff, L. and Wolfe, F. (1986). Development of criteria for the classification and reporting of osteoarthritis: Classification of osteoarthritis of the knee. Arthritis & Rheumatism, 29(8):1039-1049.

15. Angst, F., Aeschlimann, A. and Stucki, G. (2002). Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. Arthritis & Rheumatism, 45(4), pp.384-391.
16. Arden, N. and Nevitt, M., (2006). Osteoarthritis: Epidemiology, Best Practice & Research Clinical Rheumatology, 20(1): 3–25.
17. Arden, N., Lane, N., Parimi, N., Javaid, K., Lui, L., Hochberg, M. and Nevitt, M. (2009). Defining incident radiographic hip osteoarthritis for epidemiologic studies in women. Arthritis & Rheumatism, 60(4):1052-1059.
18. Arden, N.K., Blanco, F, and Cooper, C. (2015). Atlas of Osteoarthritis. Shrewbury, United Kingdom: Springer Healthcare.
19. Basaran, S., Guzel, R., Seydaoglu, G. and Guler-Uysal, F. (2010). Validity, reliability, and comparison of the WOMAC osteoarthritis index and Lequesne functional index in Turkish patients with hip or knee osteoarthritis. Clinical Rheumatology, 29(7):749-756.
20. Basford, J. (1995). Low intensity laser therapy: Still not an established tool. Lasers in Surgery and Medicine 16: 331-342.

21. Basford, J., Malanga, G., Krause, D. and Harmsen, W. (1998). A randomized controlled evaluation of low-intensity laser therapy: Plantar fasciitis. Archives of Physical Medicine and Rehabilitation, 79(3):249-254.
22. Baxter, G.D. (1994). Therapeutic Lasers: Theory and practice. Churchill Livingstone, Edinburgh.
23. Baxter, G.D., Bleakley, C., McDonough, S. (2008). Clinical effectiveness of laser acupuncture: a systematic review. Journal of Acupuncture Meridian Studies 1: 65-82.
24. Beaudreuil, J., Bendaya, S., Faucher, M., Coudeyre, E., Ribinik, P., Revel, M. and Rannou, F. (2009). Clinical practice guidelines for rest orthosis, knee sleeves, and unloading knee braces in knee osteoarthritis. Joint Bone Spine, 76(6):629-636.
25. Bennell, K. and Hinman, R. (2011). A review of the clinical evidence for exercise in osteoarthritis of the hip and knee. Journal of Science and Medicine in Sport, 14(1):4-9.
26. Bennell, K., Dobson, F. and Hinman, R. (2014). Exercise in osteoarthritis: Moving from prescription to adherence. Best Practice & Research Clinical Rheumatology, 28(1):93-117.
27. Bhatia, D., Bejarano, T. and Novo, M. (2013). Current interventions in the management of knee osteoarthritis. Journal of Pharmacy and Bioallied Sciences, 5(1), p.30.
28. Bijlsma, J. and Knahr, K. (2007). Strategies for the prevention and management of osteoarthritis of the hip and knee. Best Practice & Research Clinical Rheumatology, 21(1):59-76.

29. Bjordal, J., Couppé, C., Chow, R., Tunér, J. and Ljunggren, E. (2003). A systematic review of low level laser therapy with location-specific doses for pain from chronic joint disorders. Australian Journal of Physiotherapy, 49(2):107-116.
30. Bjordal, J., Lopes-Martins, R., Joensen, J., Couppe, C., Ljunggren, A., Stergioulas, A. and Johnson, M. (2008). A systematic review with procedural assessments and meta-analysis of Low Level Laser Therapy in lateral elbow tendinopathy (tennis elbow). BMC Musculoskeletal Disorders, 9(1).
31. Bjordal, J.M. (2012). 'Low level laser therapy (LLLT) and world association for laser therapy (WALT) dosage recommendations', Photomedicine and Laser Surgery, 30(2), 61–62.
32. Bjordal, J.M., Johnson, M.I., Iversen, V., Aimbire, F. and Lopes-Martins, R.A.B., (2006). Low-level laser therapy in acute pain: A systematic review of possible mechanisms of action and clinical effects in Randomized placebo-controlled trials, Photomedicine and Laser Surgery, 24(2), 158–168.
33. Bjordal, J.M., Johnson, M.I., Lopes-Martins, R.A.B., Bogen, B., Chow, R. and Ljunggren AE (2007). Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and meta-analysis of randomised placebo-controlled trials. BMC Musculoskeletal Disorders 8: 51.
34. Bjordal, J.M., Lopes-Martins, R.A. and Iversen, V.V. (2006). A randomised, placebo-controlled trial of low-level laser therapy for activated Achilles tendinitis with micro dialysis measurement of paratendinous prostaglandin E2 concentrations. British Journal of Sports Medicine; 40:76-80.
35. Bjordal, J.M., Lopes-Martins, R.A., Joensen, J., Couppe, C., Ljunggren, A.E., Stergioulas, A. and Johnson, M.I. (2008). A systematic review with procedural

assessments and meta-analysis of low-level laser therapy in lateral elbow tendinopathy (tennis elbow). BMC Musculoskeletal Disorders 9: 75.

36. Blagojevic, M., Jinks, C., Jeffery, A., Jordan, K.P. (2010). Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage; 18:24-33.
37. Briggs, A., Cross, M., Hoy, D., Sànchez-Riera, L., Blyth, F., Woolf, A. and March, L. (2016). Musculoskeletal Health Conditions Represent a Global Threat to Healthy Aging: A Report for the 2015 World Health Organization World Report on Ageing and Health. The Gerontologist, 56(Suppl 2), pp.S243-S255.
38. Brosseau, L., Welch, V., Wells, G., deBie, R., Gam, A., Harman, K., Morin, M., Shea, B. and Tugwell, P. (2000): Low level laser therapy (classes I, II and III) for the treatment of osteoarthritis. The Cochrane Library, Issue 2. Oxford: Update Software.
39. Brosseau, L., Welch, V., Wells, G., Tugwell, P., de Bie, R., Gam, A., Harman, K., Shea, B. and Morin, M. (2000): Low level laser therapy for osteoarthritis and rheumatoid arthritis: a meta-analysis. Journal of Rheumatology 27: 1961-1969.
40. Brosseau, S., (2005). Randomized controlled trial on low level laser therapy (LLLT) in the treatment of osteoarthritis (OA) of the hand. Lasers in Surgery and Medicine, 36(3), 210–219.
41. Brouwer, R., Huizinga, M., Duivenvoorden, T., van Raaij, T., Verhagen, A., Bierma-Zeinstra, S. and Verhaar, J. (2014). Osteotomy for treating knee osteoarthritis. Cochrane Database of Systematic Reviews.

42. Bulow, P.M., Jensen, H., Danneskiold-Samsoe, B. (1994). Low-power Ga-Al-As laser treatment of painful osteoarthritis of the knee. A double-blind placebo-controlled study. Scandinavian Journal of Rehabilitation in Medicine; 26: 155-9.
43. Campbell-Hall, V., Petersen, I., Bhana, A., Mjadu, S., Hosegood, V. and Flisher, A. (2010). Collaboration between Traditional Practitioners and Primary Health Care Staff in South Africa: Developing a Workable Partnership for Community Mental Health Services. Transcultural Psychiatry, 47(4):610-628.
44. Castaneda, S., Roman-Blas, J.A., Largo, R., and Herrero-Beaumont, G. (2012). Bone as a key target for osteoarthritis treatment. Biochemistry and Pharmacology; 83: 315-323.
45. Center for Medicare and medical aid services. Viewed 25 April 2016, from https://www.cms.gov.
46. Chaisson, C., Gale, D., Gale, E., Kazis, L., Skinner, K. and Felson, D. (2000). Detecting radiographic knee osteoarthritis: what combination of views is optimal? Rheumatology, 39(11):1218-1221.
47. Chappell, A.S., Desaiah, D., Liu-Seifert, H. (2011). A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. Pain Practice 11:33-41.
48. Cheng, D.S. and Visco, C.J. (2012). Pharmaceutical therapy for osteoarthritis. Pain Medicine and Rehabilitation; 4: S82-88.

49. Cheung, C., Wyman, J., Bronas, U., McCarthy, T., Switzer, J. and Mathiason, M. (2016). Is yoga better than aerobic/strengthening exercises for managing knee osteoarthritis in older adults? Osteoarthritis and Cartilage, 24:S484.
50. Chevalier, X. and Henrotin, Y. (2009). OARSI recommendations on knee and hip osteoarthritis. Joint Bone Spine, 76(5):455-457.
51. Chopra, A. and Abdel-Nasser, A. (2008). Epidemiology of rheumatic musculoskeletal disorders in the developing world. Best Practice & Research Clinical Rheumatology, 22(4): 583–604.
52. Chow, R.T., Heller, G.Z. and Barnsley, L, (2006). The effect of 300 mW, 830 nm laser on chronic neck pain: a double-blind, randomised, placebo-controlled study. Pain, 124:201-10.
53. Chung, H., Dai, T., Sharma, S., Huang, Y., Carroll, J. and Hamblin, M. (2012). The Nuts and Bolts of Low-level Laser (Light) Therapy. Annals of Biomedical Engineering, 40(2), pp.516-533.
54. Ciolac, E. and Greve, J. (2011). Effects of resistance exercise in older woman with knee osteoarthritis and total knee arthroplasty. Medicine and Science in Sports & Exercise, 43:754.
55. Conroy, M.B., Kwoh, C.K., Krishnan, E., Nevitt, M.C., Boudreau, R., Carbone, L.D. (2012). Muscle strength, mass, and quality in older men and women with knee osteoarthritis. Arthritis Care (Hoboken); 64: 15-21.
56. Corsinovi, L., Martinelli, E., Fonte, G. (2009). Efficacy of oxycodone/acetaminophen and codeine/ acetaminophen vs. conventional therapy in elderly women with persistent, moderate to severe osteoarthritis-related pain. Archives of Gerontology Geriatrics; 49: 378-382

57. Cotler, H. (2015). The Use of Low Level Laser Therapy (LLLT) For Musculoskeletal Pain. Orthopaedics & Rheumatology, 2(5).
58. Creswell, J. (2014). A concise introduction to mixed methods research. SAGE.
59. Cross, M., Smith, E., Hoy, D., Nolte, S., Ackerman, I., Fransen, M., Bridgett, L., Williams, S., Guillemin, F., Hill, C., Laslett, L., Jones, G., Cicuttini, F., Osborne, R., Vos, T., Buchbinder, R., Woolf, A. and March, L. (2014). The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. Annals of the Rheumatic Diseases, 73(7):1323-1330.
60. de Matos Brunelli Braghin, R., Libardi, E., Junqueira, C., Rodrigues, N., Nogueira-Barbosa, M., Renno, A. and Carvalho de Abreu, D. (2018). The effect of low-level laser therapy and physical exercise on pain, stiffness, function, and spatiotemporal gait variables in subjects with bilateral knee osteoarthritis: a blind randomized clinical trial. Disability and Rehabilitation, pp.1-8.
61. de Paula Eduardo, C., de Freitas, P.M., Esteves-Oliveira, M., Aranha, A.C., Ramalho, K.M., Simoes, A. (2010). Laser phototherapy in the treatment of periodontal disease. Laser Medicine and Science, 25:781-792.
62. De Vos, A.S., Strydom, H., Fouche, C.B. and Delport, C.S.L. 2002. Research at grass roots for the social sciences and human service professions. 2nd Ed. South Africa: Van Schaik Publishers, 140-208.
63. Dieppe, P.A., Lohmander, L.S. (2005). Pathogenesis and management of pain in osteoarthritis. Lancet, 365: 965-973.

64. Durstine, L.J., Roberts, S., Moore, G., Painter, P. and American College of Sports Medicine, (2009). ACSM's exercise management for persons with chronic diseases and disabilities. 3rd ed. Champaign, IL: Human Kinetics Publishers.
65. Egloff, C., Hugle, T. and Valderrabano, V. (2012). Biomechanics and patho-mechanisms of osteoarthritis. Swiss Medicine Weekly, 142: 13583.
66. Felson, D., McLaughlin, S., Goggins, J., LaValley, M., Gale, M., Totterman, S., Li, W., Hill, C. and Gale, D. (2003). Bone Marrow Edema and Its Relation to Progression of Knee Osteoarthritis. Annals of Internal Medicine, 139:330.
67. Felson, D.T., Lawrence, R.C., Hochberg, M.C., McAlindon, T., Dieppe, P.A., Minor, M.A. (2000). Osteoarthritis: new insights and treatment approaches. Annals of Internal Medicine, 133:726-737.
68. Field, T. (2014). Knee osteoarthritis pain in the elderly can be reduced by massage therapy, yoga and tai chi: a review. Complementary Therapies in Clinical Practice, 22:87-92.
69. Fischgrund, J. (2009). Orthopaedic Advances. Journal of the American Academy of Orthopaedic Surgeons, 17(10):601.
70. Fowler, F. (2014). Survey Research Methods (4th ed.). Sage Publications.
71. Fransen, M., Bridgett, L., March, L., Hoy, D., Penserga, E. and Brooks, P. (2011). The epidemiology of osteoarthritis in Asia. International Journal of Rheumatic Diseases, 14(2):113-121.
72. Fransen, M., McConnell, S., Harmer, A.R., Van der Esch, M., Simic, M. and Bennell, K.L. (2015). Exercise for osteoarthritis of the knee: A Cochrane systematic review. British Journal of Sports Medicine, 49(24): 1554–1557.

73. Fukuda, V., Fukuda, T., Guimarães, M., Shiwa, S., de Lima, B., Martins, R., Casarotto, R., Alfredo, P., Bjordal, J. and Fucs, P. (2015). Short-term efficacy of low-level laser therapy in patients with knee osteoarthritis: a randomized placebo-controlled, double-blind clinical trial. Revista Brasileira de Ortopedia (English Edition), 46(5), pp.526-533.
74. Fukuda, V.O., Fukuda, T.Y., Guimarães, M., Shiwa, S., de Lima, B.D.C., Martins, R.Á.B.L., Casarotto, R.A., Alfredo, P.P., Bjordal, J.M. and Fucs, P.M.M.B. (2011). Short-term efficacy of low-level laser therapy in patients with knee osteoarthritis: a randomized placebo-controlled, double-blind clinical trial. Brazillain Society of Orthopaedics and Traumatology, 46(5): 526–533.
75. Fulop, A.M., Dhimmer, S., Deluca, J.R., Johanson, D.D., Lenz, R.V and Patel, K.B. (2010). A meta-analysis of the efficacy of laser phototherapy on pain relief. Clinical Journal of Pain, 26: 729- 736.
76. Gam, A.N., Thorsen, H. and Lonnberg, F. (1993). The effect of low-level laser therapy on musculoskeletal pain: a meta-analysis. Pain, 52: 63-66.
77. Groenewald, P., Nannan, N., Bourne, D., Laubscher, R. and Bradshaw, D. (2005). Identifying deaths from AIDS in South Africa. AIDS, 19(2):193-201.
78. Grol, R. and Grimshaw, J. (2003). From best evidence to best practice: effective implementation of change in patients care. The Lancet, 362(9391):1225-1230.
79. Grotle, M., Hagen, K., Natvig, B., Dahl, F. and Kvien, T. (2008). Obesity and osteoarthritis in knee, hip and/or hand: An epidemiological study in the general population with 10 years follow-up. BMC Musculoskeletal Disorders, 9(1).

80. Gur, A., Cosut, A., Jale Sarac, A., Cevik, R., Nas, K. and Uyar, A., (2003). Efficacy of different therapy regimes of low-power laser in painful osteoarthritis of the knee: A double-blind and randomized-controlled trial. Lasers in Surgery and Medicine, 33(5): 330–338.
81. Gur, A., Cosut, A., Sarac, A.J., Cevik, R., Nas, K. and Uyar, A. (2003a). Efficacy of different therapy regimes of low-power laser in painful osteoarthritis of the knee: a double-blind and randomised controlled trial. Lasers Surgery and Medicine; 33: 330-338.
82. Gur, A., Karakoc, M., Nas, K., Cevik, R., Sarac, J. and Ataoglu, S. (2002a). Effects of low-power laser and low dose amitriptyline therapy on clinical symptoms and quality of life in fibromyalgia: a single-blind, placebo-controlled trial. Rheumatology Internals, 22: 188-193.
83. Gur, A., Karakoc, M., Nas, K., Cevik, R., Sarac, J. and Demir, E. (2002b). Efficacy of low-power laser therapy in fibromyalgia: a single-blind, placebo-controlled trial. Lasers Medicine and Science, 17: 57-61.
84. Hafsi, K., McKay, J., Li, J., Lana, J., Macedo, A., Santos, G. and Murrell, W. (2019). Nutritional, metabolic and genetic considerations to optimise regenerative medicine outcome for knee osteoarthritis. Journal of Clinical Orthopaedics and Trauma, 10(1), pp.2-8.
85. Halamka, J. (2018). The coming revolution: The healthcare challenge. Telehealth and Medicine Today, 123-134.
86. Hanoch Kumar, K. and Elavarasi, P. (2016) Definition of pain and classification of pain disorders. Journal of Advanced Clinical & Research Insights, 3(3), pp. 87–90.

87. Haq, S. and Davatchi, F. (2011). Osteoarthritis of the knees in the COPCORD world. International Journal of Rheumatic Diseases, 14(2): 122-129.
88. Harari, Y. (2017). Reboot for the AI revolution. Nature, 550(7676): 324-327.
89. Hashmi, J.T., Huang, Y.Y., Sharma, S.K., Kurup, D.B., De Taboada, L., Carroll, J.D. and Hamblin, M.R. (2010). Effect of pulsing in low-level light therapy. Lasers in Surgery and Medicine, 42: 450- 466.
90. Hassett, A. and Williams, D. (2011). Non-pharmacological treatment of chronic widespread musculoskeletal pain. Best Practice & Research Clinical Rheumatology, 25(2): 299-309.
91. Hawkeswood, J. and Reebye, R. (2010). Evidence-based guidelines for the nonpharmacological treatment of osteoarthritis of the hip and knee. British Medical Journal, 8: 399- 403.
92. Hawkins, D. and Abrahamse, H. (2007). Phototherapy: a treatment modality for wound healing and pain relief. African Journal of Biomedical Research, 10: 99-109.
93. Health-e. (2016). Health-e., Accessed 3 May 2016, from http://www.health-e.org.za/2013/07/31/the-top-5-medical-aids-in-south-africa-infographic.html.
94. Hedayat, A., Wang, J. and Xu, T. (2015). Minimum clinically important difference in medical studies. Biometrics, 71(1), pp.33-41.
95. Heidari, B. (2011). Knee osteoarthritis prevalence, risk factors, pathogenesis and features: Part I. Caspian Journal of Internal Medicine, 205-212.
96. Hernandez-Molina, G., Neogi, T., Hunter, D., Niu, J., Guermazi, A., Reichenbach, S., Roemer, F., McLennan, C. and Felson, D. (2003). The association of bone attrition with knee pain and other MRI features of osteoarthritis. Annals of the Rheumatic Diseases, 67(1): 43-47.

97. Holm, B., Kristensen, M.T., Bencke, J., Husted, H., Kehlet, H. and Bandholm, T. (2010). Loss of knee-extension strength is related to knee swelling after total knee arthroplasty. Archives of Physical Medicine and Rehabilitation, 91: 1770-1776.

98. Huber, E.O., Meichtry, A., de Bie, R.A. and Bastiaenen, C.H., (2016). Construct validity of change scores of the chair stand test versus timed up and go test, KOOS questionnaire and the isometric muscle strength test in patients with severe knee osteoarthritis undergoing total knee replacement. Manual Therapy, 21: 262–267.

99. Hutton, C. (1989). Osteoarthritis: the cause not result of joint failure. Annals of the Rheumatic Diseases, 48(11): 958-961.

100. Iwamoto. J., Sato, Y., Takeda, T. and Matsumoto, H. (2011). Effectiveness of exercise for osteoarthritis of the knee: A review of the literature. World Journal of Orthopaedics, 2: 37-42.

101. Jakobsen, T.L., Christensen, M., Christensen, S.S., Olsen, M. and Bandholm, T. (2010). Reliability of a knee joint range of motion and circumference measurements after total knee arthroplasty: does tester experience matter? Physiotherapy in Research International, 15: 126-134.

102. Javaid, M., Kiran, A., Guermazi, A., Kwoh, C., Zaim, S., Carbone, L., Harris, T., McCulloch, C., Arden, N., Lane, N., Felson, D. and Nevitt, M. (2012). Individual magnetic resonance imaging and radiographic features of knee osteoarthritis in subjects with unilateral knee pain: The Health, Aging, and Body Composition Study. Arthritis & Rheumatism, 64(10): 3246-3255.

103. Joern, W.P., Klaus, M., Brust, S. and Eysel, P. (2010). The epidemiology, eitiology, diagnosis and treatment of osteoarthritis of the knee, Cartilage, 107(9): 152-62.

104. Johannsen ,F., Hauschild, B., Remvig, L., Johnsen, V., Petersen, M. and Bieler, T. (1994). Low energy laser therapy in rheumatoid arthritis. Scandinavian Journal of Rheumatology, 23: 145-147.

105. Johnson, S. and Bulkow, B., (2005). Treatment of arthritic knee pain using photo-therapy. Journal of Geriatric Physical Therapy, 28(3):118–119.

106. Juhl, C. (2006). Short-term beneficial effects of low-level laser therapy for patients with rheumatoid arthritis. Australian Journal of Physiotherapy, 52: 224.

107. Kahn, F. (2008). Low intensity laser therapy in clinical practice. Toronto: Meditech International Inc.

108. Kazis, L., Meenan, R. and Anderson, J. (1983). Pain in the rheumatic diseases. Arthritis and Rheumatism, 26(8):1017-1022.

109. Khoshbin, A., Leroux, T., Wasserstein, D., Marks, P., Theodoropoulos, J., Ogilvie-Harris, D., Gandhi, R., Takhar, K., Lum, G. and Chahal, J. (2013). The Efficacy of Platelet-Rich Plasma in the Treatment of Symptomatic Knee Osteoarthritis: A Systematic Review with Quantitative Synthesis. Arthroscopy: The Journal of Arthroscopic & Related Surgery, 29(12), pp.2037-2048.

110. Knops, A., Vermeulen, H., Legemate, D. and Ubbink, D. (2009). Attitudes, Awareness, and Barriers Regarding Evidence-Based Surgery among Surgeons and Surgical Nurses. World Journal of Surgery, 33(7): 1348-1355.

111. Koele, R., Volker, G., van Vree, F., van Gestel, M., Köke, A. and Vliet Vlieland, T. (2014). Multidisciplinary rehabilitation for chronic widespread musculoskeletal pain: results from daily practice. Musculoskeletal Care, 12(4): 210-220.

112. Koh, Y. and Choi, Y. (2012). Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis. The Knee, 19(6), pp.902-907.

113. Koh, Y., Jo, S., Kwon, O., Suh, D., Lee, S., Park, S. and Choi, Y. (2013). Mesenchymal Stem Cell Injections Improve Symptoms of Knee Osteoarthritis. Arthroscopy: The Journal of Arthroscopic & Related Surgery, 29(4), pp.748-755.

114. Krasheninnikoff, M., Ellitsgaard, N., Rogvi-Hansen, B., Zeuthen, A., Harder, K., and Larsen, R. (1994). No Effect of Low-Power Laser in Lateral Epicondylitis. Scandinavian Journal of Rheumatology, 23: 260-263.

115. Kumar, N. (2015). Isometric exercise versus combined concentric-eccentric exercise training in patients with osteoarthritis knee. International Journal of Physiotherapy, 2(6).

116. Laupattarakasem, W., Laopaiboon, M., Laupattarakasem, P. and Sumananont, C. (2008). Arthroscopic debridement for knee osteoarthritis. Cochrane Database of Systematic Reviews.

117. Lee, M.S. and Ernst, E. (2011). Acupuncture for pain: An overview of Cochrane Reviews. China Journal of Integrated Medicine, 17: 187-9.

118. Lewis, M. and Johnson, M. (2006). The clinical effectiveness of therapeutic massage for musculoskeletal pain: a systematic review. Physiotherapy, 92(3), pp.146-158.

119. Litwic, A., Edwards, M., Dennison, E. and Cooper, C. (2013). Epidemiology and burden of osteoarthritis. British Medical Bulletin, 105(1): 185-199.

120. Lopes-Martins, R., Penna, S.C., Joensen, J., Iversen, V.V. and Bjordal, J.M. (2006). Low level laser therapy (LLLT) in inflammatory and rheumatic diseases: A review of therapeutic mechanisms. Current Rheumatology Reviews, 3: 147-154.

121. Maeda, T., Yoshida, H., Sasaki, T. and Oda, A. (2017). Does transcutaneous electrical nerve stimulation (TENS) simultaneously combined with local heat and cold applications enhance pain relief compared with TENS alone in patients with knee osteoarthritis. Journal of Physical Therapy Science, 29(10): 1860-1864.

122. Majima, T., Inoue, M., Kasahara, Y., Onodera, T., Takahashi, D. and Minami, A. (2012). Effect of the Japanese herbal medicine on the osteoarthritis of the knee with joint effusion. Sports Medical Rehabilitation and Therapeutic Technology; 4: 3.

123. Marshall, C., Dobson, F., Hinman, R., Sayer, T., Anderson, C., Newcomb, N. and Bennell, K. (2015). Reliability of the osteoarthritis research society international recommended performance-based tests of physical function in people with hip and knee osteoarthritis. Osteoarthritis and Cartilage, 23: A343-A344.

124. Massardo, L., Watt, I., Cushnaghan, J. and Dieppe, P. (1989). Osteoarthritis of the knee joint: an eight year prospective study. Annals of the Rheumatic Diseases, 48(11): 893-897.

125. McAlindon, T., Bannuru, R., Sullivan, M., Arden, N., Berenbaum, F., Bierma-Zeinstra, S., Hawker, G., Henrotin, Y., Hunter, D., Kawaguchi, H., Kwoh, K., Lohmander, S., Rannou, F., Roos, E. and Underwood, M. (2015). Corrigendum to '2014 OARSI Guidelines for the Non-Surgical Management of Knee Osteoarthritis' [Osteoarthritis and Cartilage 22 (2014) 363–388]. Osteoarthritis and Cartilage, 23(6), pp.1026-1034.

126. Mester, A. and Mester, A. (2017). The History of Photobiomodulation: Endre Mester (1903–1984). Photomedicine and Laser Surgery, 35(8): 393-394.

127. Mester, E., Mester, A.F. and Mester, A. (1985). The biomedical effects of laser application. Lasers Surgery in Medicine; 5: 31-39.

128. Microsoft (2016) 'Excel'.

129. Murray, C. and Lopez, A. (1997). Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. The Lancet, 349(9064), pp.1498-1504.

130. Musumeci, G., Mobasheri, A., Trovato, F., Szychlinska, M., Imbesi, R. and Castrogiovanni, P. (2016). Post-operative rehabilitation and nutrition in osteoarthritis. F1000 Research, 116.

131. Orozco, L., Munar, A., Soler, R., Alberca, M., Soler, F., Huguet, M., Sentís, J., Sánchez, A. and García-Sancho, J. (2013). Treatment of Knee Osteoarthritis with Autologous Mesenchymal Stem Cells. Transplantation Journal, 95(12), pp.1535-1541.

132. Palazzo, C., Nguyen, C., Lefevre-Colau, M., Rannou, F. and Poiraudeau, S. (2016). Risk factors and burden of osteoarthritis. Annals of Physical and Rehabilitation Medicine, 59(3): 134-138.

133. Panton, L., Simonavice, E., Williams, K., Mojock, C., Kim, J.S. and Kingsley, J.D. (2012). Effects of class IV laser therapy on fibromyalgia impact and function in women with fibromyalgia. Journal of Alternative and Complementary Medicine, 19: 445-452.

134. Pas, H., Winters, M., Haisma, H., Koenis, M., Tol, J. and Moen, M. (2017). Stem cell injections in knee osteoarthritis: a systematic review of the literature. British Journal of Sports Medicine, 51(15), pp.1125-1133.

135. Patel, S., Dhillon, M., Aggarwal, S., Marwaha, N. and Jain, A. (2013). Treatment With Platelet-Rich Plasma Is More Effective Than Placebo for Knee Osteoarthritis. The American Journal of Sports Medicine, 41(2), pp.356-364.

136. Pearson, J., Walsh, N., Carter, D., Koskela, S. and Hurley, M. (2016). Developing a web-based version of an exercise-based rehabilitation program for people with chronic knee and hip pain: A mixed methods study. JMIR Research Protocols, 5(2): e67.

137. Peat, G., McCarney, R. and Croft, P. (2001). Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Annals of Rheumatology Disorder, 60: 91-97.

138. Pfleger, B. (2007). Burden and control of musculoskeletal conditions in developing countries: a joint WHO/ILAR/BJD meeting report. Clinical Rheumatology, 26(8):1217-1227.

139. Pisters, M.F., Veenhof, C., van Meeteren, N.L., Ostelo, R.W., de Bakker, D.H., Schellevis, F.G. and Dekker, J. (2007). Long-term effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a systematic review. Arthritis and Rheumatology, 57: 1245-1253.

140. Quintana, J.M., Escobar, A., Arostegui, I., Bilbao, A., Azkarate, J., Goenaga, J.I. and Arenaza, J.C. (2006). Health-related quality of life and appropriateness of knee or hip joint replacement. Archives of Internal Medicine, 166(2): 220.

141. Radtke, T., Puhan, M., Hebestreit, H. and Kriemler, S. (2016). The 1-min sit-to-stand test—a simple functional capacity test in cystic fibrosis? Journal of Cystic Fibrosis, 15(2): 223-226.

142. Rayegani, S., Raeissadat, S., Heidari, S. and Moradi-Joo, M. (2017). Safety and Effectiveness of Low-Level Laser Therapy in Patients with Knee Osteoarthritis: A Systematic Review and Meta-analysis. Journal of Lasers in Medical Sciences, 8(Suppl 1), pp.S12-S19.

143. Reeves, S., Perrier, L., Goldman, J., Freeth, D. and Zwarenstein, M. (2013). Inter-professional education: effects on professional practice and healthcare outcomes. Cochrane Database of Systematic Reviews.

144. Reid, C., Bush, P., Cummings, N., McMullin, D. and Durrani, S. (2010). A review of occupational knee disorders. Journal of Occupational Rehabilitation, 20(4): 489-501.

145. Ringdahl, E. and Pandit, S. (2011) Treatment of Knee Osteoarthritis. American family physician, 83 (11), pp.1287-1292.

146. Ronn, K., Reischl, N., Gautier, E. and Jacobi, M. (2011). Current surgical treatment of knee osteoarthritis. Arthritis, 2011: 454873.

147. Roos, E. and Arden, N. (2015). Strategies for the prevention of knee osteoarthritis. Nature Reviews Rheumatology, 12(2): 92-101.

148. Roos, E.M., Roos, H.P., Lohmander, L.S., Ekdahl, C. and Beynnon, B.D., (1998). Knee injury and osteoarthritis outcome score (KOOS)—

Development of a self-administered outcome measure. Journal of Orthopaedic and Sports Physical Therapy, 28(2): 88–96.

149. Salaffi, F., Leardini, G., Canesi, B., Mannoni, A., Fioravanti, A., Caporali, R., Lapadula, G. and Punzi, L. (2003). Reliability and validity of the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index in Italian patients with osteoarthritis of the knee. Osteoarthritis and Cartilage, 11(8): 551-560.

150. Sharma, L. (2001). The role of knee alignment in disease progression and functional decline in knee osteoarthritis. Journal of American Medical Association, 286(2): 188.

151. Silverwood, V., Blagojevic-Bucknall, M., Jinks, C., Jordan, J., Protheroe, J. and Jordan, K. (2015). Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthritis and Cartilage, 23(4): 507-515.

152. Skou, S., Roos, E., Laursen, M., Rathleff, M., Arendt-Nielsen, L., Simonsen, O. and Rasmussen, S. (2015). A Randomized, Controlled Trial of Total Knee Replacement. New England Journal of Medicine, 373(17), pp.1597-1606.

153. Smith, K. (2005). Laser (and LED) therapy is phototherapy. Photomedicine and Laser Surgery, 23(1): 78-80.

154. Smith, K.C. (2010). Laser and LED photobiology. Laser Therapy, 19: 72-78.

155. Soleimanpour, H., Gahramani, K., Taheri, R., Golzari, S., Safari, S., Esfanjani, R. and Iranpour, A. (2014). The effect of low-level laser therapy on

knee osteoarthritis: prospective, descriptive study. Lasers in Medical Science, 29(5): 1695-1700.

156. Solomon, L., Beighton, P., Valkenburg, H. and Robin, G. (1975). Rheumatoid arthritis in the South African Negro. Annals of the Rheumatic Diseases, 34(5): 463-464.

157. Soni, A., Batra, R., Gwilym, S., Spector, T., Hart, D., Arden, N., Cooper, C., Tracey, I. and Javaid, M. (2013). Neuropathic Features of joint pain: a community-based study. Arthritis and Rheumatism, 65(7): 1942-1949.

158. Speetzen, S. J. (2018) Nursing Capstones Department of Nursing An Anti-inflammatory Diet in Osteoarthritis Prevention & Management Recommended Citation. Nursing capstones, 148(2).

159. Stemberger, R. and Kerschan-Schindl, K. (2013). Osteoarthritis: physical medicine and rehabilitation--non-pharmacological management. Wiener Medizinische Wochenschrift, 163: 228-235.

160. Strong, J. (2002). Chronic pain problems. A Textbook for Therapists. London: Churchill Livingstone, pp 397- 410.

161. Sturgill, L.P., Snyder-Mackler, L., Manal, T.J. and Axe, M.J. (2009). The interrater reliability of a clinical scale to assess knee joint effusion. Journal of Orthopaedic Sports and Physical Therapy, 39: 845-849.

162. Szabo, G., Lovasz, G., Kustos, T. and Bener, A. (2000). A prospective comparative analysis of mobility in osteoarthritic knees: Does lifestyle have an influence? Bone and Joint Journal, Nov 1; 82(8):1167-1169.

163. Tascioglu, F., Armagan, O., Tabak, Y., Corapci, I. and Oner, C. (2004). Low-power laser treatment in patients with knee osteoarthritis. Swiss Medical Weekly, 134: 254-258.

164. Tascioglu, F., Degirmenci, N.A., Ozkan, S. and Mehmetoglu, M. (2012). Low-level laser in the treatment of carpal tunnel syndrome: clinical, electrophysiological, and ultra-sonographic evaluation. Rheumatology International, 32: 409-415.

165. Thorsen, H., Gam, A.N., Svensson, B.H., Jess, M., Jensen, M.K., and Piculell, I. (1992). Low level laser therapy for myofascial pain in the neck and shoulder girdle. A double-blind, cross-over study. Scandinavian Journal of Rheumatology, 21: 139-141.

166. TIBCO Software. (2017) 'Statistica v13.3'. StatSoft Inc.

167. Tollman, S., Kahn, K., Sartorius, B., Collinson, M., Clark, S. and Garenne, M. (2008). Implications of mortality transition for primary health care in rural South Africa: a population-based surveillance study. The Lancet, 372(9642): 893-901.

168. Tomazoni, S., Leal-Junior, E., Pallotta, R., Teixeira, S., de Almeida, P. and Lopes-Martins, R. (2017). Effects of photobiomodulation therapy, pharmacological therapy, and physical exercise as single and/or combined treatment on the inflammatory response induced by experimental osteoarthritis. Lasers in Medical Science, 32(1), pp.101-108.

169. Towheed, T., Maxwell, L., Judd, M., Catton, M., Hochberg, M. and Wells, G. (2006). Acetaminophen for osteoarthritis. Cochrane Database of Systematic Reviews.

170. Trelles, M., Rigau, J., Sala, P., Calderhead, G. and Ohshiro, T. (1994). Infrared Diode laser in low reactive Low Laser Therapy (LLLT) for knee osteoarthritis. Laser Therapy, 3: 149-153.

171. Tugwell, P.S., Wells, G.A. and Shainhouse, J.Z. Equivalence study of a topical diclofenac solution compared with oral diclofenac in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. (2004). Journal of Rheumatology, 31:2002-2012.

172. Usenbo, A., Kramer, V., Young, T. and Musekiwa, A., (2015). Prevalence of arthritis in Africa: A systematic review and Meta-Analysis. Peer-reviewed Open Access Scientific Journal- Medicine, 10(8).

173. Vaishya, R. (2019). Regeneration is better than the replacement. Journal of Clinical Orthopaedics and Trauma, 10(1), p.1.

174. Van Rensch, P., Van de Pol, G., Goosen, J., Wymenga, A. and De Man, F. (2014). Arthrodesis of the knee following failed arthroplasty. Knee Surgery, Sports Traumatology, Arthroscopy, 22(8), pp.1940-1948.

175. Vogt, W. and Johnson, B. (2011). Dictionary of statistics & methodology. Thousand Oaks, Calif: SAGE.

176. Walach, H., Güthlin, C. and König, M. (2004). Efficacy of Massage Therapy in Chronic Pain: A Pragmatic Randomized Trial. The Journal of Alternative and Complementary Medicine, 9(6), pp.837-846.

177. Watson, P. (2000). Physical activities programme content in pain management: An Interdisciplinary Approach. London, Churchill Livingstone; 285-301.

178. Williams, V., Piva, S., Irrgang, J., Crossley, C. and Fitzgerald, G. (2012). Comparison of Reliability and Responsiveness of Patient-Reported Clinical Outcome Measures in Knee Osteoarthritis Rehabilitation. Journal of Orthopaedic & Sports Physical Therapy, 42(8), pp.716-723.

179. Woolf, A. (2015). Global burden of osteoarthritis and musculoskeletal diseases. BMC Musculoskeletal Disorders, 16(S1).

180. Yousefi-Nooraie, R., Schonstein, E., Heidari, K., Rashidian, A., Pennick, V., Akbari-Kamrani, M., Irani, S., Shakiba, B., Mortaz Hejri, S., Jonaidi, A. and Mortaz-Hedjri, S. (2008). Low level laser therapy for nonspecific low-back pain. Cochrane Database of Systematic Reviews.

181. Zhang, L., Xing, D., Gao, X. and Wu, S. (2009). Low-power laser irradiation promotes cell proliferation by activating PI3K/AKT pathway. Journal of Cellular Physiology, 219: 553-562.

182. Zhang, W. (2010). Risk factors of knee osteoarthritis--excellent evidence but little has been done. Osteoarthritis Cartilage, 18: 1-2.

183. Zhang, W., Doherty, M., Peat, G., Bierma-Zeinstra, M., Arden, N., Bresnihan, B., Herrero-Beaumont, G., Kirschner, S., Leeb, B., Lohmander, L., Mazieres, B., Pavelka, K., Punzi, L., So, A., Tuncer, T., Watt, I. and Bijlsma, J. (2009). EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. Annals of the Rheumatic Diseases, 69(3): 483-489.

184. Zhang, W., Nuki, G. and Moskowitz, R.W. (2010). OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage, 18:476-499.

185. Zhang, Y. and Jordan, J. (2010). Epidemiology of Osteoarthritis. Clinics in Geriatric Medicine, 26(3): 355-369.

186. Zhou, Z., Liu, Y., Chen, H. and Liu, F. (2014). Body mass index and knee osteoarthritis risk: A dose-response meta-analysis. Obesity, 22(10): 2180-2185.

APPENDIX 1: ETHICAL CLEARNACE CERTIFICATE

R14/49 Ms Aayesha Kholvadia et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M1611112

NAME: (Principal Investigator)	Ms Aayesha Kholvadia et al
DEPARTMENT:	Centre for Exercise Science and Sports Medicine University of the Witwatersrand Unit 1, 322 Flamingo Street, Ext 6, Lenasia
PROJECT TITLE:	Exercise Training and Low Level Laser Therapy as a Modulate to Pain Relief and Functional Changes in Osteoarthritis
DATE CONSIDERED:	25/11/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Demitri Constantinou and Dr Phillippe Gradidge
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	10/03/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review November and will therefore be due in the month of November each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 10/03/2017

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 2: LETTER TO MEDICAL SCHEMES REGARDING THE INCIDENCE OF KNEE OSTEOARTHIRITIS

To whom it may concern

Hello, my name is Aayesha Kholvadia. I am a PhD candidate based at the Centre for Exercise Science and Sports Medicine at the University of the Witwatersrand. I am conducting research to explore the effects of exercise and Low Level Laser therapy (LLLT) on knee osteoarthritis (KOA).

You are requested to participate in a study whereby we aim to document the incidence and treatment prescription of knee osteoarthritis within a South African setting. We will be using low level laser in isolation or as an adjunct to exercise therapy for patients suffering with knee osteoarthritis. It is important that you are aware of the fact that the study has been approved by the Human Research Ethics Committee (HREC) at the University of the Witwatersrand.

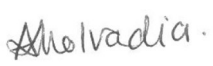
The data on the prevalence of knee osteoarthritis within a South African context is scarce and not current; this study therefore aims at bridging the gap in literature by documenting and updating the incidence of knee osteoarthritis and its treatment profile. This information will assist in the field of diagnosing and effectively treating knee osteoarthritis. We have chosen 11 ICD-10 codes which are commonly associated with knee osteoarthritis and ask you to please provide us with statistics on medical aid claims over your last fiscal year for the following ICD-10 codes or by

running an automated printout on the number of claims against each of these codes over the last fiscal year:

ICD -10 CODE	ICD -10 CODE DESCRIPTION	# OF CLAIMS
M17.0	Bilateral primary osteoarthritis of the knee	
M17.10	Unilateral primary osteoarthritis, unspecified knee	
M17.11	Unilateral primary osteoarthritis, right knee	
M17.12	Unilateral primary osteoarthritis, left knee	
M17.2	Bilateral post-traumatic osteoarthritis of knee	
M17.30	Unilateral post-traumatic osteoarthritis, unspecified knee	
M17.31	Unilateral post-traumatic osteoarthritis, right knee	
M17.32	Unilateral post-traumatic osteoarthritis, left knee	
M17.4	Other bilateral secondary osteoarthritis of knee	
M17.5	Other unilateral secondary osteoarthritis of knee	
M17.9	Osteoarthritis of knee, unspecified	

Furthermore, I would like to offer you/your company a personal meeting at your convenience. Once all our data has been received and collated the finalised protocol will be available from me or my research supervisors. We thank you for your time.

Yours Sincerely



Aayesha Kholvadia

Principal researcher / PhD candidate:

(082 972 8307) / a.kholvadia@gmail.com

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

APPENDIX 3: STUDY OUTLINE – MEDICAL PRACTITIONER

STUDY OUTLINE: MEDICAL PRACTITIONER

Dear Medical Practitioner

Hello, my name is Aayesha Kholvadia. I am a PhD candidate based at the Centre for Exercise Science and Sports Medicine at the University of the Witwatersrand. I am conducting research to explore the effects of exercise and Low Level Laser therapy (LLLT) on knee osteoarthritis (KOA).

You are being requested to participate in a research study by:

1. Completing a questionnaire on your practice's current treatment regime for knee osteoarthritis, and by
2. Referring prospective participants to the study

The study aim is to investigate the prevalence, management strategies and intervention of exercise and LLLT on knee osteoarthritis. To attain the aim above the following objectives have been set:

1. To investigate the prevalence of KOA in South Africa
2. To underline the current management of KOA in the above-mentioned region
3. To establish the effects of exercise and LLLT on the functional components of KOA within the southern areas of Johannesburg, South Africa.

It is important to note that ethical approval for the study has been obtained from the Human Research Ethics Committee (HREC) at the University of the Witwatersrand.

For further information, contact:

Chair of the Committee	Prof Peter Cleaton Jones	011 717 2301	peter.cleaton-jones1@wits.ac.za
Administrative Officers	Ms Z Ndlovu	011 717 2700 / 2656/ 1234/ 1252	zanele.ndlovu@wits.ac.za
	Mr. Rhulani Mkansi		rhulani.mkansi@wits.ac.za
	Mr. Lebo Moeng		lebo.moeng@wits.ac.za

If you are willing to participate, please take some time to complete the questionnaire below:

	Number	**Percentage**
What number and percentage of diagnosed knee osteoarthritis patients are seen in your practice on a monthly basis?		
What number and percentage of these diagnosed knee osteoarthritis patients have bilateral knee osteoarthritis?		

Tick the appropriate box regarding your knee osteoarthritis patients:

Most often suggested treatment mode	Pharmacological	Surgical	Homeopathic	Exercise rehabilitation	Low level laser therapy

Please mark a single appropriate section regarding your opinion on the therapies and interventions mentioned below:

	Strongly agree	**Agree**	**Disagree**	**Strongly disagree**
Pharmacological interventions are effective for the treatment of knee osteoarthritis.				
Knee osteoarthritis patients are compliant with their **pharmacological** intervention.				
Surgical interventions are effective for the treatment of knee osteoarthritis.				
Knee osteoarthritis patients are compliant with their **surgical** intervention.				
Homeopathic interventions are effective for the treatment of knee osteoarthritis.				
Knee osteoarthritis patients are compliant with their **homeopathic** intervention				
Biokinetics / Physiotherapy interventions are effective for the treatment of knee osteoarthritis.				
Knee osteoarthritis patients are compliant with their **Biokinetics / Physiotherapy** interventions.				
Low Level Laser therapy is effective for the treatment of knee osteoarthritis.				
Knee osteoarthritis patients are compliant with their **Low Level Laser therapy** sessions.				

Additionally, I would like to request you to please refer patients between the ages of 40-75yrs who are diagnosed with knee osteoarthritis, whom in your opinion would be suitable candidates for the study. These patients should have no previous history of

cancer, epilepsy or an open wound on the knee. Furthermore, pregnant females would be excluded from the study.

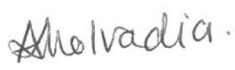
The use of Low level laser therapy has shown to address pain and joint function by using a single beam of red and infra-red light (300-900nm) eliciting photochemical changes in the cell. These changes then translate to a reduction of pain and inflammation at the treated joint. The current literature trends focus on pharmacological or surgical interventions for the treatment of knee osteoarthritis, therefore this study aims at exploring changes to the knee joint post low level laser therapy exposure as a holistic functional mode of treatment.

The table below highlights some of the key factors pertaining to participation in the study:

Aim: To investigate the prevalence, management strategies and intervention of exercise and LLLT on knee osteoarthritis.
Procedure: The participant will have to undergo a pre-test assessment, followed by a 12-session intervention and assessment at the end of session 6 and session 12 and a 1 and 3-month post intervention follow-up. Furthermore, the participant will be required to attend 12 sessions of intervention with the researcher. Appointments will be scheduled between the researcher and the participant selected to attend these sessions.
Possible risks: There are no risks to participation in the study as the low level laser therapy is pain free, non-toxic and non-thermal.
Possible Benefits: As a result of participation in this study, the participant may expect to have an improvement in knee osteoarthritis symptoms as well as an improvement in functionality.
Costs incurred: Participation in this study will not result in any additional cost to the participant.
Confidentiality: The participant's identity will not be evident on any data sheets or revealed in any discussion, description or scientific publications by the investigators.
Access to findings: Any new information or benefit that develops during the course of the study will be shared by the researcher.

If anything is not clear, please feel free to ask me for clarification and I would like to thank you in advance for partaking in this study.

Yours Sincerely



Aayesha Kholvadia

Principal researcher / PhD candidate:

(082 972 8307) / a.kholvadia@gmail.com

APPENDIX 4: DATA RECORDING / EVALUATION SHEET

Sample Group: (X the appropriate box)

Low level laser therapy	Low level laser therapy + exercise	Exercise

Participant code: ☐ **Treated knee** LEFT ☐ RIGHT ☐

Intervention										
Markers	**Pre test**		**Mid test**		**Post test**		**1-month post intervention**		**3-month post intervention**	
Knee Circumference										
Proximal patella (mm)	(L)	(R)	(L)	(R)	(L)	(R)	(L)	(R)	(L)	(R)
Mid Patella (mm)	(L)	(R)	(L)	(R)	(L)	(R)	(L)	(R)	(L)	(R)
Distal patella (mm)	(L)	(R)	(L)	(R)	(L)	(R)	(L)	(R)	(L)	(R)
Western Ontario and McMaster Universities Arthritis Index (WOMAC)										
WOMAC Score / total										
Knee range of motion										
Knee extension (°)	(L)	(R)	(L)	(R)	(L)	(R)	(L)	(R)	(L)	(R)
Knee flexion (°)	(L)	(R)	(L)	(R)	(L)	(R)	(L)	(R)	(L)	(R)
Additional comments:										
Physical functionality test										
Timed sit-to-stand (reps)										

Intervention sessions:

Date #1	Date #2	Date #3	Date #4	Date #5	Date #6
Date #7	Date #8	Date #9	Date #10	Date #11	Date #12

Additional Remarks

Exercise:

Medical precaution:

Laser:

APPENDIX 5: WESTERN ONTARIO AND MCMASTER UNIVERSITIES ARTHRITIS INDEX (WOMAC) SCORE

This survey requests for your view about your knee. The information will assist the researcher in identifying your reaction to your knee functionality (Roos et al, 1998).

Answer every question by ticking the appropriate box

SYMPTOMS

These questions should be answered thinking about your knee during the **last week**

S1. Do you have swelling in your knee?				
Never	Rarely	Sometimes	Often	Always
S2. Do you feel grinding; hear clicking or any other type of noise when your knee moves?				
Never	Rarely	Sometimes	Often	Always
S3. Does your knee catch or hung up when moving?				
Never	Rarely	Sometimes	Often	Always
S4. Can you straighten your knee fully?				
Never	Rarely	Sometimes	Often	Always
S5. Can you bend your knee fully?				
Never	Rarely	Sometimes	Often	Always

STIFFNESS

The following questions concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease at which you move your knee joint.

S6. How severe is your knee joint stiffness after first waking in the morning?				
None	Mild	Moderate	Severe	Extreme
S7. How severe is your knee stiffness after sitting, laying or resting **later in the day?**				
None	Mild	Moderate	Severe	Extreme

PAIN

P1. How often do you experience knee pain?				
Never	Monthly	Weekly	Daily	Always
P2. What amount of knee pain have you experienced the **last week** during the following activities?				
Twisting or pivoting on your knee				
None	Mild	Moderate	Severe	Extreme
P3. Straightening the knee fully				
None	Mild	Moderate	Severe	Extreme
P4. Bending the knee fully				
None	Mild	Moderate	Severe	Extreme
P5. Walking on a flat surface				
None	Mild	Moderate	Severe	Extreme
P6. Going up or down stairs				
None	Mild	Moderate	Severe	Extreme
P7. At night while in bed				
None	Mild	Moderate	Severe	Extreme
P8. Sitting or lying				
None	Mild	Moderate	Severe	Extreme
P9. Standing upright				
None	Mild	Moderate	Severe	Extreme

FUNCTION – DAILY LIVING

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A1. Descending stairs				
None	Mild	Moderate	Severe	Extreme
A2. Ascending stairs				
None	Mild	Moderate	Severe	Extreme
A3. Rising from sitting				
None	Mild	Moderate	Severe	Extreme
A4. Standing				
None	Mild	Moderate	Severe	Extreme
A5. Bending to the floor to pick up an object				
None	Mild	Moderate	Severe	Extreme
A6. Walking on a flat surface				
None	Mild	Moderate	Severe	Extreme
A7. Getting in / out of a car				
None	Mild	Moderate	Severe	Extreme
A8. Going shopping				
None	Mild	Moderate	Severe	Extreme
A9. Putting on socks / stockings				
None	Mild	Moderate	Severe	Extreme
A10. Rising from bed				
None	Mild	Moderate	Severe	Extreme
A11. Taking off socks / stocking				
None	Mild	Moderate	Severe	Extreme
A12. Lying in bed – turning over, maintaining knee position				
None	Mild	Moderate	Severe	Extreme
A13. Getting in / out of a bath				
None	Mild	Moderate	Severe	Extreme
A14. Sitting				
None	Mild	Moderate	Severe	Extreme
A15. Getting on / off the toilet				

None	Mild	Moderate	Severe	Extreme

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A16. Heavy domestic duties – moving heavy boxes, scrubbing floors etc.				
Never	Rarely	Sometimes	Often	Always
A17. Light domestic duties – cooking, dusting etc.				
Never	Rarely	Sometimes	Often	Always

Thank you for completing all the questions in this questionnaire.

Your WOMAC score is:	

Reference for score:

(http://www.orthopaedicscore.com/scorepages/knee_injury_osteopaedic_outcome_score_womac.html).

APPENDIX 6: LOW LEVEL LASER THERAPY OUTLINE

The table below depicts the treatment and progression for participants in the low level laser therapy group and participants in the low level laser therapy placebo group:

Low level laser therapy session outline

	SESSION 1,2,3,4			SESSION 5,6,7,8			SESSION 9,10,11,12		
TREATMENT HEAD	FREQUENCY	DUTY CYCLE	DURATION (min)	FREQUENCY	DUTY CYCLE	DURATION (min)	FREQUENCY	DUTY CYCLE	DURATION (min)
SLD-R 500	CW		6/6/6	100	90	6/6/6	1000-5000	80-90	7/7/7
SLD-I 1000	50	50-90	6/6/6	250	80	7/7/7	250-1000	90	8/8/8
LD- I 200	CW		6	CW		6	CW	90	6

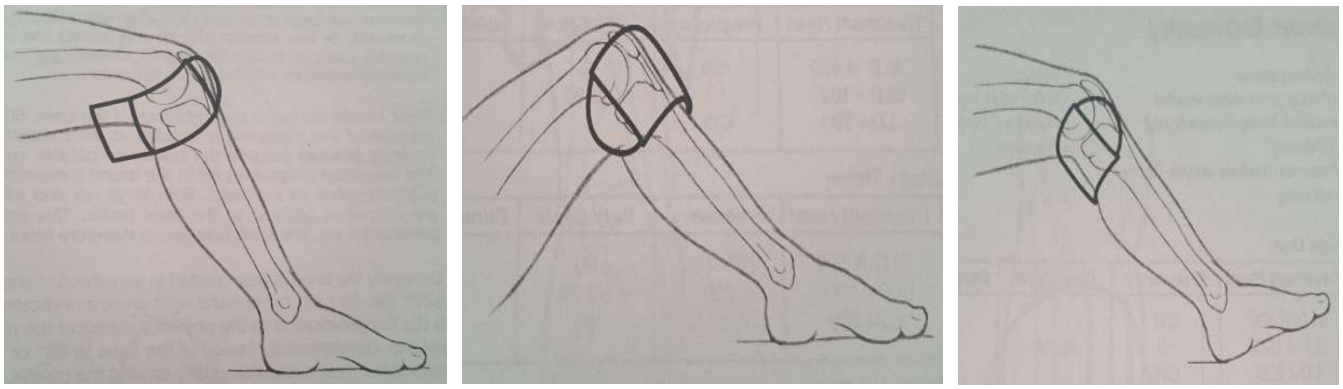


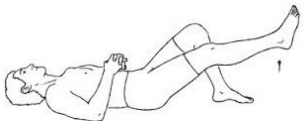
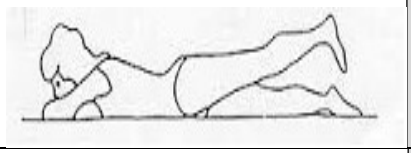
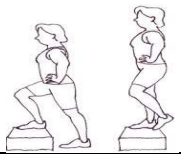
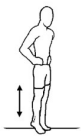
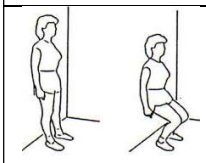
Fig.1: 3 laser array placements

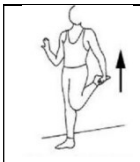
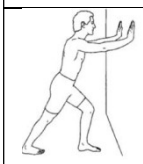
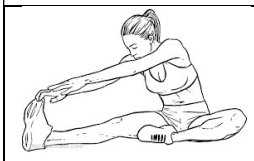

SLD-I 1000
LDI 200
CPU unit
SLD-R 500

APPENDIX 7: EXERCISE THERAPY OUTLINE

The table below depicts the exercises and progression of exercises to be performed for the low level laser therapy, and exercise and low level laser therapy placebo, and exercise groups:

It is important to note that participants unable to complete the required number of reps or sets of the initial session will be progressed according to their individual abilities. All this data will be noted by the researcher on the data recording sheet.

		SESSION 1,2,3,4		SESSION 5,6,7,8		SESSION 9,10,11,12	
		REPS	SETS	REPS	SETS	REPS	SETS
	QUAD SETTING	12	1	12	2	0	0
	SUPINE SLR	12	1	12	2	15	2
	BALL SQUEEZES	12	1	12	2	15	2
	PRONESIDE LEG RAISE	12	1	12	2	15	2
	STEP UPS	0	0	10	2	15	2
	CALVE RAISE	12	1	12	2	15	2
	WALL SQUATS	0	0	10	1	12	2
	SINGLE LEG BALANCE	0	0	10	1	12	2

	**QUAD STRETCH**	1	30sec	1	30 sec	2	1
	**CALVE STRETCH**	1	30sec	1	30 sec	2	1
	**HAMSTRING STRETCH**	1	30sec	1	30 sec	2	1

*All pictures have been extracted from exercise prescription software (Physio advisor -http://www.physioadvisor.com.au/) that the researcher is subscribed to.

APPENDIX 8: STUDY OUTLINE FOR THE PARTICIPANT

Dear participant

Hello, my name is Aayesha Kholvadia. I am a PhD candidate based at the Center for Exercise Science and Sports Medicine at the University of the Witwatersrand. I am doing research to explore the effects of exercise and low level laser therapy on knee osteoarthritis.

You have been requested to participate in this research study. We are going to provide information that will assist in understanding the purpose and aims. This document will also explain what you will be requested to do during the study, the risks and the benefits of the study, and your rights as a participant in this research study. If anything is unclear, please feel free to contact the researcher (Aayesha Kholvadia) for clarification.

Informed consent and voluntary participation

To participate in this project, it will be required of you to sign a written consent form that will include a signature, dates and initials, in order to confirm that you understand and agree to the conditions of participation in the study for a period of 12 sessions.

You have the right to query concerns regarding the study at any time. You are encouraged to report any new problems during the study, to the researcher (Aayesha

Kholvadia). Telephone numbers and other contact numbers have been provided. Please feel free to utilise these numbers.

Participation in this study is completely voluntary. This means that you are not obligated to take part in any research should you feel uncomfortable. If you choose not to participate, your present and /or future medical care will not be affected in any way and you will not incur any penalty and/or loss of benefits to which you may otherwise be entitled.

Ethical approval for the study

It is important that you are aware that the study has been approved by the Human Research Ethics Committee (HREC) at The University of the Witwatersrand. This is a group of independent experts whose responsibility is to help ensure that the right and welfare of the participants in research are protected and that the study is carried out in an ethical manner. This committee can also answer any questions about your rights as a research participant.

You may contact the Chair of the Committee, Prof Peter Cleaton Jones on 011 717 2301 or peterpeter.cleaton-jones1@wits.ac.za for further clarification should you feel it necessary.

Confidentiality

You have the right to privacy. Although your identity will at all times remain confidential, the result of the research study may be presented at scientific conferences or in a specialist publication. The researcher (Aayesha Kholvadia) will keep information

about your participation in secure coded files with your name removed. All data will be anonymised before it is analysed, meaning that your name and any identifying information will be removed.

Study outline

As a patient diagnosed with knee osteoarthritis, you will be eligible for the study. The battery of tests mentioned will be performed before you start, repeated after session number 6 and session number 12, furthermore you will be asked to complete a simple questionnaire at the end of session 3, 6, 9,12, 1 and 3-month post intervention. All these tests will be conducted by the researcher (Aayesha Kholvadia).

These tests include: a measuring tape to measure knee circumference, a questionnaire depicting your pain (Western Ontario and McMaster Universities Arthritis Index -WOMAC scale), a goniometer test to measure knee range of motion, and a 1-minute functionality test. Once your initial battery of tests is complete, you will then be allocated to your respective sample group. You will be required to complete 12 sessions of low level laser therapy with / without exercise with the researcher (depending on your group). Individual appointments will be scheduled with you personally to attend these sessions. Furthermore, you will be requested to complete a 1 and 3-month follow up session with the researcher a month after you have completed your intervention testing.

If you fail to follow the prescribed process, or if your medical condition changes in a manner that the researcher believes it is not in your best interest to continue in this study, or for administrative reasons, your participation may be discontinued. All data

received will be kept strictly confidential. The study may be terminated at any time by the researcher, study supervisors, or the HREC that initially approved it.

Possible risks

The laser is pain free, non-toxic and has no thermal effects.

Possible benefits

Benefits that may be apparent to you during the study include a reduction in pain and a general improvement in functionality.

Costs to you

Participating in the research will involve no cost to you.

Please feel free to contact me at any time with study related queries on 011 852 8903 or 0829728307 or a.kholvadia@gmail.com.

Yours Sincerely



Aayesha Kholvadia

(Principal researcher)

APPENDIX 9: INFORMATION SHEET AND INFORMED CONSENT FORM

TITLE OF THE RESEARCH PROJECT	Exercise training and LLLT as a modulate to pain relief and functional changes in KOA
PRINCIPAL INVESTIGATOR	Aayesha Kholvadia
ADDRESS	Unit 1 322 Flamingo street Ext 6 Lenasia 1820
CONTACT DETAILS	011 852 8903 / 0829728307 a.kholvadia@gmail.com

DECLARATION BY OR ON BEHALF OF PARTICIPANT:
I, (*the undersigned participant*) _____ (*name/surname*) _____ (*I D number*) of _____ (*address*) _____ (*contact number)*

THE FOLLOWING ASPECTS HAVE BEEN EXPLAINED TO ME, THE PARTICIPANT:	
Aim: To investigate the prevalence, management strategies and intervention of exercise and LLLT on knee osteoarthritis.	Initial
Procedure: As the participant, you will have to undergo a pre-test assessment, followed by a 12-session intervention and assessment at the end of session 6 and session 12 and a 1 and 3-month post intervention follow-up. Furthermore, the participant will be required to attend 12 sessions of intervention with the researcher. Appointments will be scheduled between the researcher and the participant selected to attend these sessions.	Initial

Possible risks: There are no risks to participation in the study as the low level laser therapy is pain free, non-toxic and non-thermal.	Initial
Possible Benefits: As a result of my participation in this study, I may expect to have an improvement in knee osteoarthritis symptoms as well as an improvement in functionality.	Initial
Costs incurred: Participation in this study will not result in any additional cost to me.	Initial
Confidentiality: My identity will not be evident on any data sheets or revealed in any discussion, description or scientific publications by the investigators.	Initial
Access to findings: Any new information or benefit that develops during the course of the study will be shared with me.	Initial

Voluntary participation/refusal/discontinuation: My participation is voluntary, and I can withdraw at any time: ☐ YES ☐ NO My decision whether or not to participate will in no way affect my present or future medical care: ☐ TRUE ☐ FALSE No pressure was exerted on me to consent to participation and I understand that I may withdraw at any stage without penalization.	Initial
I HEREBY CONFIRM THE FOLLOWING:	
I, the participant, was invited to participate in the above-mentioned research project which is being undertaken by Aayesha Kholvadia.	Initial
The information above was explained to me/the participant by Aayesha Kholvadia in English/Afrikaans and I am in command of this language.	Initial
I was hereby given the opportunity to ask questions and all these questions were answered satisfactorily.	Initial

I hereby confirm that I have given consent to voluntary participation in the study on the

effects of low level laser therapy on knee osteoarthritis conducted by the researcher (Aayesha Kholvadia) as outlined in the explained protocol.

Signed / confirmed _____
(*Signature*)
At_____
(*Place*)
On_____
(*Date*)
Witness by _____ _____
(*Name*) (*Signature*)

STATEMENT BY THE RESEARCHER (AAYESHA KHOLVADIA):

I, Aayesha Kholvadia (ID: 8311060123083) declare that I have explained the information in the document and study outline to: _____ (*participant*); he/she was encouraged and provided sufficient time to ask questions. The conversation was conducted in English or Afrikaans where necessary. I have provided the participant with my contact details and explained that I may be contacted at any time for matters relating to participation in this study.

Signed / confirmed

_____

(*signature*)

At_____

(*place*)

On_____

(*date*)

Witness by _____ _____

(*name*) (*signature*)

APPENDIX 10: CO-AUTHOR PERMISSION

Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, **Aayesha Kholvadia,** student number **1588653**, declare that this **Thesis** is my own work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my Thesis/Dissertation/Research Report.

Signature of Student Kholvadia. **Date** 26 March 2019

Name of Primary Supervisor 1: Prof D Constantinou

Signature of Primary Supervisor

……**Date**……

Name of Primary Supervisor 1: Dr P Gradidge

Signature of Primary Supervisor

……**Date**……

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article(s) by the student as part of his/her Thesis/Dissertation/Research Report. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for his/her degree purposes.

Article 1: Title: The efficacy of low level laser therapy and exercise for knee osteoarthritis

Journal name, year, volume and page numbers: South African Journal of Sport Medicine

Authors	Name	Signature	Date
1st author	Aayesha Kholvadia		26 March 2019
2nd author			
3rd author			