Biomarkers in Osteoarthritis

by

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(Medical Research)

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Supervisors

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Statement of Originality

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

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Statement of Co-Authorship

This thesis includes papers for which Oliver Stannus (OS) was not the sole author. OS was the lead in the research of each manuscript; however, he was assisted by the co-authors, whose contributions are detailed below.

Chapter 4:

The contribution of each author:
OS was responsible for data management and cleaning, carried out analysis and interpretation of data, prepared the initial manuscript draft and completed manuscript revisions.
GJ and FC designed and carried out the study planning, participated in analysis and interpretation of data and critically revised the manuscript.
QS participated in analysis and interpretation of data and critically revised the manuscript.
DD critically revised the manuscript.
CD designed and carried out the study planning, participated in analysis and interpretation of data, assisted with the initial manuscript draft and critically revised the manuscript.
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The contribution of each author:

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QS participated in analysis and interpretation of data and critically revised the manuscript.
VP and JB carried out data collection and critically revised the manuscript.
CD designed and carried out the study planning, was responsible for data collection, participated in analysis and interpretation of data, assisted with the initial manuscript draft and critically revised the manuscript.

Chapter 6:

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OS was responsible for data management and cleaning, carried out analysis and interpretation of data, prepared the initial manuscript draft and completed manuscript revisions.
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LB participated in analysis and interpretation of data and critically revised the manuscript.
CD designed and carried out the study planning, was responsible for data collection, participated in analysis and interpretation of data, assisted with the initial manuscript draft and critically revised the manuscript.
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The contribution of each author:
OS and JC are co-first authors on this paper. They were responsible for data management and cleaning, carried out analysis and interpretation of data, prepared the initial manuscript draft and critically revised the manuscript.
CD designed and carried out the study planning, was responsible for data collection, participated in analysis and interpretation of data and critically revised the manuscript.
FC designed and carried out the study planning, participated in analysis and interpretation of data and critically revised the manuscript.
GJ designed and carried out the study planning, participated in analysis and interpretation of data, assisted with the initial manuscript draft, critically revised the manuscript and completed manuscript revisions.

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OS and YC are co-first authors on this paper. They carried out analysis and interpretation of data and prepared the initial manuscript draft. OS also collected the data for this paper and was responsible for data management and cleaning.
GJ designed and carried out the study planning, participated in analysis and interpretation of data and critically revised the manuscript.
LB participated in analysis and interpretation of data and critically revised the manuscript.
BA critically revised the manuscript.
CD designed and carried out the study planning, participated in analysis and interpretation of data, assisted with the initial manuscript draft and critically revised the manuscript.
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DJ participated in analysis and interpretation of data and critically revised the manuscript.

FC designed and carried out the study planning, participated in analysis and interpretation of data and critically revised the manuscript.

YC critically revised the manuscript.

CD designed and carried out the study planning, participated in analysis and interpretation of data, assisted with the initial manuscript draft and critically revised the manuscript.

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Statement of Ethical Conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.
Abstract

Osteoarthritis (OA) is a multifactorial disease of the joints, common among older adults, which can lead to pain, impaired function and reduced quality of life. This thesis aims to investigate the associations and predictive value of various hormonal, inflammatory and imaging biomarkers with OA outcomes in population-based studies of people with and without prevalent OA.

Two population samples were used in this thesis. The first group was a population-based sample of older adults aged 50-80 years (mean age: 62 years; 51% female). Followup measurements were conducted 2.7 (2.6-3.3) years later and again for questionnaire data 5.0 (5.3-6.8) years later. Magnetic resonance imaging (MRI) on the right knees was undertaken at baseline and first followup: knee cartilage volume, tibial bone area, cartilage defects and bone marrow lesions (BMLs) were measured or scored; cartilage mean T1 signal intensity and thickness were measured by semi-automated software. Baseline knee and hip x-rays were scored for joint space narrowing (JSN) and osteophytes. Serum leptin and cytokine levels were measured by immunoassay at baseline and first followup. Body morphometry was measured at baseline. Fat and lean mass measures were measured at baseline using dual-energy x-ray absorptiometry (DXA). Knee pain was assessed by questionnaires (WOMAC, Western Ontario and McMaster Osteoarthritis Index) at all timepoints.

The second group was a population-based sample of younger adults aged 26-51 (mean age 41; 64% female). Anthropometric, x-ray and MRI-derived scores and measures were obtained as in the first group. Urinary C-terminal crosslinking telopeptide of type II collagen (U-CTX-II) was measured by immunoassay.

This thesis consists of 6 studies. In the first study, in older adults, circulating levels of both leptin and interleukin-6 (IL-6) were associated with hip JSN in both sexes and females respectively, independently of BMI. Adiposity was associated with hip JSN, but not after adjustment for leptin.

In the second study, baseline levels of both IL-6 and tumor necrosis factor alpha (TNF-α) were associated with medial tibiofemoral knee JSN. Baseline IL-6, change in IL-6 and change in TNF-α were associated with cartilage volume loss.

In the third study, in older adults, baseline or change over 2.9 years in circulating levels of high sensitivity C-reactive protein (hs-CRP), IL-6 and TNF-α were associated with change over 5 years in sub-scale or total WOMAC knee pain.
In the fourth study, higher leptin in older adults was significantly associated with lower femoral, tibial and patellar cartilage thickness. Fat measures were negatively associated with cartilage thickness, largely mediated by leptin. Baseline and change in leptin were associated with medial tibial cartilage thickness loss.

In the fifth study, knee cartilage defects in older adults were found to be common, not likely to regress, and to predict cartilage volume loss and risk of knee replacement.

In the final study, mean T1 MRI signal intensity of cartilage was negatively associated with BMI and same-region cartilage defects in younger and older adults; with U-CTX-II in younger adults; and with JSN and osteophytes in older adults at various sites. It predicted cartilage thickness loss over 2.7 years in older adults.

In conclusion, inflammatory and metabolic factors may play important roles in aetiology of cartilage loss and/or symptoms in OA. Cartilage defects predict cartilage loss and risk of knee replacement, and mean T1 MRI signal intensity of cartilage predicts loss of cartilage thickness. All these are potential biomarkers for OA at risk of development or progression, and thus possible targets for intervention.
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Other Publications

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Wellington, New Zealand
(Oral presentation)

2009  World Congress on Osteoarthritis (Osteoarthritis Research Society International Annual Meeting)
Serum levels of inflammatory markers, knee radiographic osteoarthritis, and knee cartilage loss in older adults
Montreal, Canada
(Oral presentation - presented by co-author)

2009  World Congress on Osteoarthritis (Osteoarthritis Research Society International Annual Meeting)
The associations between leptin, interleukin-6 and hip radiographic osteoarthritis in older people
Montreal, Canada
(Oral presentation - presented by co-author)

2011  Australian Rheumatology Association Annual Scientific Meeting
Cartilage signal intensity on MRI: association with body mass index, cartilage defects and type II collagen breakdown
Brisbane, Australia
(Poster presentation - Best basic science poster prize)

2011  World Congress on Osteoarthritis (Osteoarthritis Research Society International Annual Meeting)
Inflammatory biomarkers are predictive of increases in knee pain over 5 years in older adults
San Diego, USA
2011  Australian Rheumatology Association Annual Scientific Meeting

*Inflammatory biomarkers are predictive of increases in knee pain over 5 years in older adults*

Brisbane, Australia

(Poster presentation)

2011  Osteoarthritis Research Society International Imaging Meeting

*Cartilage signal intensity on MRI: association with body mass index, cartilage defects and type II collagen breakdown*

Salzburg, Austria.

(Poster presentation)

2012  American College of Rheumatology Annual Meeting

*Cross-sectional and longitudinal associations between circulating leptin and knee cartilage thickness in older adults*

Washington DC, USA

(Oral presentation - presented by co-author)
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<td>2D</td>
<td>two-dimensional</td>
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<tr>
<td>BIPED</td>
<td>burden, investigative, prognostic, efficacy or diagnostic</td>
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<tr>
<td>BLOKS</td>
<td>Boston–Leeds osteoarthritis score</td>
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<td>BME</td>
<td>bone marrow edema</td>
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<td>BMI</td>
<td>body mass index</td>
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<td>BML</td>
<td>bone marrow lesion</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<td>COMP</td>
<td>cartilage oligomeric protein</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>CTX-II</td>
<td>C-terminal crosslinking telopeptide of type II collagen</td>
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<tr>
<td>CV</td>
<td>coefficient of variation</td>
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<tr>
<td>DALY</td>
<td>disability-adjusted life year</td>
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<tr>
<td>dGEMRIC</td>
<td>delayed gadolinium-enhanced MRI of cartilage</td>
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<tr>
<td>DMOAD</td>
<td>disease modifying anti-osteoarthritis drug</td>
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<tr>
<td>DXA</td>
<td>dual energy x-ray absorpiometry</td>
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<tr>
<td>FSE</td>
<td>fast spin echo</td>
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<tr>
<td>GEE</td>
<td>generalised estimating equation</td>
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<tr>
<td>GRE</td>
<td>gradient recall echo</td>
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<tr>
<td>HOAMS</td>
<td>hip osteoarthritis MRI scoring system</td>
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<tr>
<td>hs-CRP</td>
<td>high-sensitivity C-reactive protein</td>
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<tr>
<td>IFN-γ</td>
<td>interferon gamma</td>
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<tr>
<td>IL-1</td>
<td>interleukin 1</td>
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<td>IL1-β</td>
<td>interleukin 1-beta</td>
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<td>IL-6</td>
<td>interleukin 6</td>
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<td>JSN</td>
<td>joint space narrowing</td>
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<td>KCVS</td>
<td>knee cartilage volume study</td>
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<td>KL</td>
<td>Kellgren–Lawrence</td>
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<tr>
<td>KOSS</td>
<td>knee osteoarthritis scoring system</td>
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<tr>
<td>MMP</td>
<td>matrix-metalloproteinase</td>
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<td>MOAKS</td>
<td>MRI knee osteoarthritis score</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>NO</td>
<td>nitric oxide</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>NOS</td>
<td>nitric oxide synthase</td>
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<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
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<tr>
<td>OA</td>
<td>osteoarthritis</td>
</tr>
<tr>
<td>OARSI</td>
<td>osteoarthritis research society international</td>
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<tr>
<td>OHA-MRI</td>
<td>Oslo hand osteoarthritis MRI score</td>
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<tr>
<td>OP</td>
<td>osteophyte</td>
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<tr>
<td>QALY</td>
<td>quality-adjusted life year</td>
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<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
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<tr>
<td>ROA</td>
<td>radiographic osteoarthritis</td>
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<tr>
<td>ROI</td>
<td>region of interest</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>TASOAC</td>
<td>Tasmanian older adult cohort</td>
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<tr>
<td>THR</td>
<td>total hip replacement</td>
</tr>
<tr>
<td>TJR</td>
<td>total joint replacement</td>
</tr>
<tr>
<td>TKR</td>
<td>total knee replacement</td>
</tr>
<tr>
<td>TNF-α</td>
<td>tumor necrosis factor alpha</td>
</tr>
<tr>
<td>uCTX-II</td>
<td>urinary C-terminal crosslinking telopeptide of type II collagen</td>
</tr>
<tr>
<td>WHR</td>
<td>waist–hip ratio</td>
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<tr>
<td>WOMAC</td>
<td>Western Ontario and McMasters pain questionnaire</td>
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<td>WORMS</td>
<td>whole organ magnetic resonance imaging score</td>
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