Outcome of osteoarthritis and arthroplasty from patient perspective to molecular profiling.

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Introduction

Predictors of joint disease and outcome of arthroplasty from patient perspective to molecular profiling.

The average life expectancy is increasing, and it is predicted that by 2045 over 30% of the population in the Western World will be aged over 60 years of age. With older age, health deteriorates and the prevalence of most chronic diseases increases, however, the extend of these diseases varies between men and women.[1] Loss of independency at higher age is most often due to problems of the musculoskeletal system (MSK). Out of all rheumatic diseases, osteoarthritis (OA) is the most frequent cause of these MSK problems, which may cause severe disability of patients. OA is the most prevalent chronic joint disorder worldwide, affecting the joints of hip, knee, hands, spine and feet and is strongly influenced by metabolic health and age.[2-4]

In short, OA is characterized by deterioration of the cartilage of the joint and leads to narrowing of the joint space until the presence of bare bone on bone contact and the formation of osteophytes.[5] Of the 291 conditions studied in the Global Burden of Disease study, OA ranks as the 11th highest contributor to global disability and has been found to be the leading source of morbidity (i.e. pain and functional disability) in industrialized countries.[6,7] Incidence and prevalence vary widely depending upon the used definition and sampled population.[8,9] Knee OA is more prevalent than hip OA with an estimated global prevalence of radiographically confirmed knee OA of 3.8% (95%CI: 3.6-4.1), while for hip OA this was 0.85% (95%CI: 0.74-1.02%).[10,11] In the Netherlands, the average prevalence of osteoarthritis is 5.7% in males and 10.4% in females, affecting more often the knee than the hip.[12]

In 2007, the health care costs of joint related diseases in the Netherlands, including osteoarthritis, were estimated at 2.1 billion euro, 3.6% of the national medical costs.[13] By 2015, the total direct costs attributable to osteoarthritis alone were 1.3 billion euro, which was 1.6% of the total healthcare costs for the Netherlands in 2015.[14] Thus, adequate treatment and the adequate selection of patients to undergo treatment is paramount to keep public healthcare affordable in the near future.

Efficient treatment is hampered by the heterogeneity of this disease; the disassociation of radiographic and clinical symptoms makes the diagnosis a container of diverse pathological processes. Currently, no cure exists to halt the progression of osteoarthritis and treatment consists of pain relief and minimizing the impact on functioning in daily life.

Patients will start with pain medication such as analgesics, intra articular steroids and/or intra articular hyaluronic in order to relieve their symptoms.[15-18] As these medications only affect the symptoms of OA, they do not slow down the progression of the disease. When the symptoms have become too severe and pain medication is not sufficient anymore, arthroplasty will be performed. Arthroplasty is a major invasive surgery during which the joint is replaced by an implant.

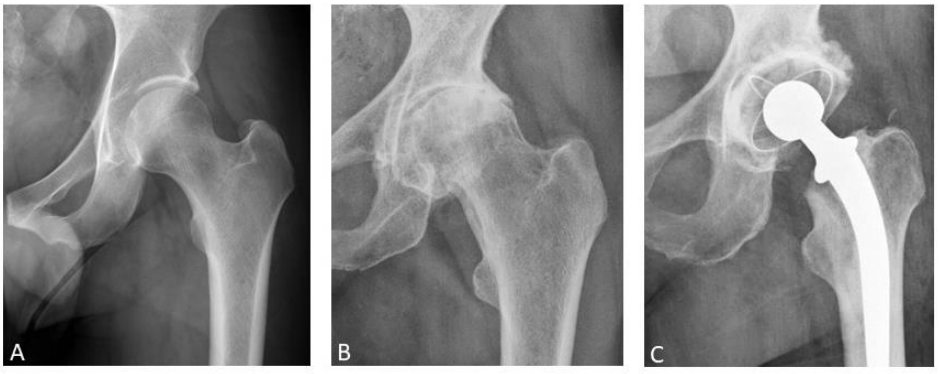

Figure 1 - Rontgen photos of (A) a healthy hip joint, (B) an osteoarthritic hip joint and (C) a hip joint after total joint replacement (arthroplasty) surgery.

In the Netherlands, 29,937 total hip arthroplasty (THA) and 29,221 total joint arthroplasty (TKA) surgeries were performed in 2017.[19] The procedure is very safe and effective with a mean survival rate of a hip or knee prosthesis of 95% at 15 years after surgery.[20-24] Despite these excellent results with respect to revision of the knee or hip prostheses, patients perceived satisfaction varies. While some patients are very satisfied (mean 83 points out of 100 on a visual analog scale), a large group (up to 20%) is not satisfied with their surgery.[25-28]

Postsurgery factors associated with outcome of joint arthroplasty: prosthesis and physical activity.

Reasons for this large portion of less favorable outcomes are multifactorial and can be related to surgical factors (i.e. surgical technique), joint status (i.e. deformity or degree of osteoarthritis) but also patient factors, like preoperative patient expectations, patient selection and baseline health status. The latter will also be associated with the metabolic state of the patient, thus determining recovery and rehabilitation after a surgical intervention, like a total joint arthroplasty, which has a tremendous impact on a patient. Next to this, other preoperative factors related to metabolic health, affecting muscle function (i.e. mitochondrial function) will also have an effect on postoperative recovery and thus rehabilitation after a major surgical procedure.

This is underscored even more, since the majority of the patients who have total joint arthroplasty at the age of about 70 years have one or more comorbidities, resulting in higher perioperative risks with concomitant less favourable outcome of TJA surgery. Finally, outcome after TJR can be affected by the total joint arthroplasty itself, which is related to foreign body reactions to wear debris produced by the artificial new joint. In this thesis, we assess three main factors that are related with the outcome; (I) the implant, (II) physical activity and (III) baseline health of the patient.

I Bearings of prostheses (implants).

Many designs and types of hip and knee prostheses are available, not only with different shapes but also with different types of bearings. One of these bearings is a metal-on-metal bearing used in total hip replacement, with the idea that it is more durable (i.e. less wear) than a metal on polyethylene bearing. Since metal-on-metal (MOM) bearings produce metal wear debris, causing both local and systemic adverse effects (e.g. nephrotoxicity or cardiotoxicity), these implants are no to be used.[29] However, since these MOM hip prostheses are still in place thousands of patients, a discussion on long-term effects of these implants on patients is important.

II Postoperative physical activity

One of the main hallmarks of successful total joint arthroplasty is its actual use, as is reflected by the level of physical activity (PA) of the patients. Postoperative rehabilitation is essential to have an optimal postoperative result since both muscle strength as well as range of motion of the joint after the arthroplasty will affect PA.[30] The literature on PA after arthroplasty up to now is conflicting and an age-matched comparison with the general population of postoperative PA is lacking.

III Baseline health of the patient

Since OA is prevalent especially among elderly patients, their preoperative baseline health varies considerably. The heterogeneity in baseline health status can be measured in many different ways.[31] Here we discuss to what extent the baseline frailty index, a standardized measurement of handgrip strength or molecular profiling associate with the outcome.

Baseline health factors associated with outcome of joint arthroplasty: frailty index, handgrip strength & molecular profiling.

III A Frailty

In the Netherlands, up to 83% of the THA patients and 79% of TKA patients are 60 years and older.[19] As frailty is highly prevalent in the elderly, with a prevalence of 10.7% in this age group, it is likely that a considerable proportion of patients undergoing THA or TKA are frail.[32] This may have an effect on recovery after a TJA and thus the functional outcome after such an intervention.

Although there is not one definition for frailty, the most often used definitions include a combination of decrease of independence, strength, cognition, activity, energy, weight and walking speed.[33-39] Considerable heterogeneity in the extent of frailty between individuals is present, with some persons accelerating fast while others are slowly progressing to more severe levels of frailty.[40] Between persons of the same age, the onset of frailty differs greatly per individual. The pooled prevalence rates for persons aged 65-69 is less than 5%, while for those aged 80-85 this is over 15% and even over 25% for persons aged ≥85.[41-44]

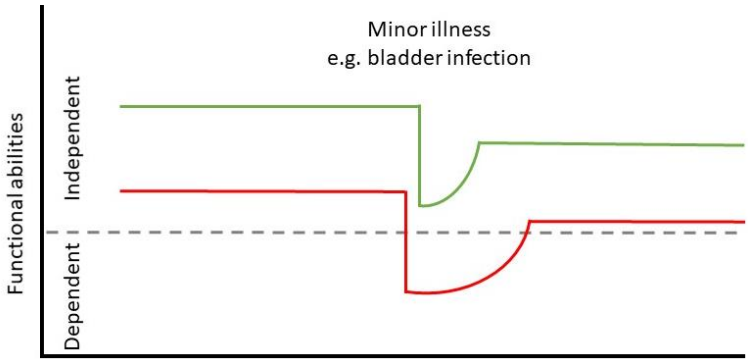

Figure 2 – Capability to resist stressors such as a minor illness. Certain persons can maintain a level of independence in their functional abilities whereas others are strongly affected by a minor illness and need a long recovery phase.

Frailty represents less resilience, with less capability to resist stressors, and thus reflects overall health and functional status of an individual, as simplified in figure 2. As such frailty might be associated with less favorable outcome after arthroplasty surgery (i.e. a cause for the 15-20% less favourable results after hip- and knee arthroplasty surgery).[41,45-47] Frailty can be assessed by means of a validated questionnaire, and in order to assess the role of frailty in the outcome of total joint surgery, we used the self-reported Groningen Frailty Indicator (GFI) questionnaire to classify patients as frail or non-frail.[48]

III B Handgrip strength

As the GFI is a self-reported questionnaire, one can also assess the prognostic value of a more objective measure, handgrip strength (HGS). HGS is a proxy for overall muscular strength and is associated with worse general health and all-cause mortality.[49-55] In various patient groups, HGS has been shown to be a predictor for disability, malnutrition and surgery complications.[56-65] Also, HGS may reflect a degree of sarcopenia, the loss of skeletal muscle. Sarcopenia is relatively common in eldely, with prevalence of up to 50% in those aged over 80.[66] The relation of preoperative HGS and changes of hip and knee function and quality of life after arthroplasty needs more investigation.

III C Metabolic Health

Variation in the baseline health status of elderly patients is strongly determined by their immune and metabolic health. With the increased lifespan of the world population, as well as increasing levels of metabolically compromised and obese individuals and sedentary lifestyles, the baseline health of elderly decreases and the incidence and the burden on society of OA will increase as a consequence. Years of biomedical ageing research, predominantly in animal models, has recently made progress into understanding how immune and metabolic health varies and influences the individual ageing and disease rates (e.g. by accumulation of senescent cells, blood born factors and damaged proteins). [40]

This research resulted in novel treatment strategies for OA, currently being testing in clinical trials. The field is, however, in need of new biomarkers that may classify which baseline risks would require such treatment. Defining biomarkers for ageing and how these affect the onset and progression of diseases and of outcome of interventions like THA or TKA, would enhance patient specific treatment option. Biomarker research may also increase knowledge on the primary physiological processes underlying OA. For personalized medicine, it is paramount to increase our understanding of osteoarthritis as well as to find proper markers of predictive and prognostic value.

Epidemiological studies have shown associations of OA with unfavorable metabolic parameters, such as high body mass index (BMI), waist hip ratio and proportion of fat mass, which are especially features of metabolic diseases, such as hypertension, obesity and diabetes mellitus.[68-75] In concordance with this, weight loss reduces the symptoms of OA, relieves the pain and increases the physical function of people with OA.[76-79]

For hip and knee OA, this association is partly explained by increased mechanical load; however, also an association of high BMI and hand OA, a non-weight bearing joint, has been found.[80,81] The latter suggests a connection between OA and obesity beyond axial loading.[82,83] Furthermore, the association of OA with classical markers

of poor metabolic health such as LDL-cholesterol indicates that the metabolic health of individuals affects susceptibility for OA.[84-86] Currently, more and more evidence is emerging linking OA to the metabolic syndrome.[87-91]

To increase our understanding of the relationship of OA with baseline metabolic health more intense analyses of metabolism are required, for example by measuring metabolites in the circulation. Metabolites, the intermediate end products of metabolism, represent the influence of genotype, phenotype and environment on cell, tissues and organ functions. Novel metabolomics assays may assist in estimating the metabolic health of individuals. Such assays, as for example the well-standardized ^{1}H-Nuclear Magnetic Resonance (NMR) based plasma metabolite assays, detect a fraction of the blood metabolome and can be applied to estimate the relation between baseline metabolic health and OA disease risk.

Thus, a metabolite profile which differs between OA patients and healthy persons may reflect the aetiology of OA, the metabolites may refer to pathways that causally contributed to the OA process. Alternatively, such differences may reflect (be a biomarker of) the baseline health status of patients indicative of the resilience to recover from arthroplasty and may be part of the puzzle to explain the 15-25% of adverse outcome after a total hip- or knee arthroplasty in these OA patients.

Outline of this thesis

This thesis addresses several characteristics (potential (bio)markers), tested for their association with outcome after a total hip or knee arthroplasty. Characteristics of different nature were included: material of prosthesis, physical activity, questionnaires, clinical measures and metabolomics. This thesis aims to evaluate some of these aspects related to outcome of arthroplasty, from patient perspectives to molecular profiling (e.g. metabolic health).

First, in **chapter 2**, a meta-analysis as well as a systematic review was performed in order to assess the mortality in patients with metal-on-metal total hip prostheses as compared to patients with non-metal-on-metal total hip prostheses. Following, in **chapter 3**, the level of physical activity in hip and knee prosthesis patients was compared to the general population in order to get an indication of the actual 'use' of the prosthesis.

We then focused on baseline health factors such as frailty index, handgrip strength and molecular profiling. In **chapter 4**, the Groningen Frailty Indicator (GFI) was validated for patients scheduled to undergo hip or knee arthroplasty. Subsequently, in **chapter 5**, the GFI was applied in order to assess whether it can be used as a prognostic factor for functional outcome after hip or knee arthroplasty. Since the GFI is a subjective questionnaire, a more objective measure such as handgrip strength was assessed in similar fashion in **chapter 6**.

Finally, in **chapter 7** metabolomics-profiling was used to identify possible biomarkers of OA and OA-progression. This type of biomarker may contribute to a prognostic tool to select patients who will benefit substantially from arthroplasty. Additionally such a biomarker may lead to a more profound understanding of the pathophysiology of OA.

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