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

Meessen, J.M.T.A.

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Summary & General Discussion

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With increasing life expectancy, the incidence and burden of osteoarthritis on society will increase. Currently, no treatment of end-stage symptomatic osteoarthritis is available and when symptoms become too severe a total joint arthroplasty (TJA) will be performed, replacing the affected joint with a prosthesis. Although replacement surgery of the hip (THA) or knee (TKA) is safe and commonly performed, up to 20% of the patients are unsatisfied with the outcome.[1-3] The exact reasons for this dissatisfaction are unknown but may vary from the type of surgical procedure itself, expectancy of the outcome of arthroplasty surgery to the patient's preoperative state of overall metabolic health.

This thesis aimed to evaluate some of these aspects related to outcome of TJA, from patient perspectives to molecular profiling (e.g. metabolic health). Characteristics of different nature were included: material of prosthesis, physical activity, questionnaires, clinical measures and metabolomics. This holistic approach enables the assessment of more patient specific targets such as advices on treatment modalities. Ultimately, selection of patients, both from a patient's as well as orthopaedic surgeon's perspective, will be optimised for the best intervention (either conservative or surgical) for a specific patient. Since osteoarthritis is currently the major driver for performing TJA, the conclusion of this thesis will spark future studies into OA and its overall effect on disability.

Post-surgery factors associated with outcome of joint arthroplasty: prosthesis and physical activity.

I Bearings of prostheses

Arthroplasty surgery with an implant aims to create a functional painless joint which has been destructed by a degenerative disease or even trauma. The overall success rate at 10 year follow-up show a mean hip or knee implant survival of 95%, resulting in the classification of total hip prosthesis as the operation of century.[4] There are many types of implants and within each type a multitude on designs of implants or prostheses are on the market. Each design claims to have their own specific benefits. One such type of hip-prosthesis is the metal-on-metal bearing total hip prosthesis (MoM THA), as with any artificial joint replacement, wear is present upon moving the joint. The wear particles of the MoM THA are submicron metal debris particles (mostly chromium and cobalt particles), causing not only local, but also systematic reactions. For those reasons, the Netherlands Orthopaedic Association advised against its use since 2012, whilst further research was done.

The overall systematic effect, defined as mortality, of these metal particles was assessed by means of a meta-analysis of articles on metal-on-metal total hip prostheses, including 47 papers. The overall methodological quality of these papers was moderate. All studies suffered from allocation concealment problems and often patients, caregivers and outcome assessors were not blinded to the treatment. In addition, the observational studies clearly suffered from confounding by indication. However, all studies had a 100% compliance with the treatment as is inevitable with any implanted joint, as well as high levels of skills and experience by the surgeons. As shown in **Chapter 2,** at 10 year follow-up, there is an increased risk of mortality in patients with MoM THA as compared to patients with non-MoM THA: 8.5% risk difference (95%CI: 5.8% - 11.2%). The fact that for patients with less than 10-year follow-up we did not observe this mortality difference indicates a probable dose-response association for exposure to metal particles. This dose-response association is supported by a meta-regression analysis showing that the duration of follow-up was the only effect modifier.

This severe adverse effect of metal-on-metal prostheses has been demonstrated by studies describing cobalt-poisoning in patients with MOM prostheses, of whom the symptoms were relieved upon removal of the prosthesis.[5-7] On top of this, the International Agency for Research on Cancer (IARC) classified chromium as “carcinogenic to humans” and cobalt as “possibly-carcinogenic to humans”.[8] Surely, exposure to chromium has been demonstrated to elevate the risk to develop lung, sinonasal and stomach cancer.[9-11] Unfortunately, we did not have any information on the cause of death of patients with MOM prosthesis in our systematic review.

The exact effects of the exposure to the metal-ions-cocktail of chromium and cobalt for MOM patients are not clear yet, warranting further research into the dose-response association of person/hip years exposure to MOM THA.[12] In addition, close monitoring of patients with a MOM THA prosthesis implanted is paramount.

II Postoperative physical activity

A successful total joint arthroplasty indicates that patients experience an extensive reduction in pain, have a better mobility of the joint and consequently experience more functionality (e.g. improved daily activities). How this relates to their peers in the general population was evaluated in **Chapter 3**. The functionality of THA and TKA patients was compared with the general population, using the level of physical activity (PA), as a measure of functionality.

We assessed both the minutes per week spent on a particular type of physical activity as well as the overall adherence to the Dutch guideline for physical activity (NNGB, 5 days per week more than 30 minutes of moderate intensity physical activity) between both groups.

Interestingly, THA and TKA patients adhere more often to the NNGB than the general Dutch population, when correcting for age, sex, BMI and education level (THA: OR 1.79, 95%CI: 1.26-2.56; TKA: OR 1.73, 95%CI: 1.20-2.51). Even more, patients who had a hip arthroplasty in the preceding 6-22 months spent more minutes on overall physical activity as compared to the general Dutch population (13.8% increase, 95%CI: 1.60-27.6%, P=0.024). For TKA, also an increase in the min/week on physical activity was observed, however this did not reach statistical significance (11.2% increase, 95%CI: -1.4 – 25.6%, P=0.084).

The increased level of PA in THA and TKA patients may be explained by postoperative physiotherapy, making them more prone to adhere to a more active lifestyle or may be to the memory of lost mobility in the preoperative state, thus underscoring the importance of maintaining mobility for overall functionality. Low-impact sports such as hiking or cycling are protective against function loss and pain associated with OA whereas heavy loading sports may be risk factors for developing OA as well as early implant failure.[13-17] More studies into the impact of physical activity on the development and prevention of OA as well as the recovery of joint replacement surgery are necessary to optimize patient care.

The level of physical activity in this study was based on validated self-reported questionnaires. As is known from several studies, a discrepancy exists between outcomes of questionnaires and more objective measures such as accelerometers. Indeed a systematic review on physical activity after THA or TKA measured by accelerometers found that arthroplasty patients were less physically active than our findings which were assessed by questionnaires.[18]

A study by Sabia *et al.*[19] found that this discrepancy between self-reported activity and accelerometer registered activity is dependent on socio-economic status (SES), with persons with a higher SES having a greater correlation between self-reported and accelerometer measured level of physical activity. Budget constrains science to rely on self-reported physical activity, however with increasing technological progress, data on physical activity may in the near future be collected by means of apps at the patient's mobile devices.

III Baseline health of the patient

As the life expectancy is increasing, the prevalence of OA will increase and subsequently also the number of performed total joint arthroplasties will increase. In the Netherlands, total hip arthroplasty has increased from 23.000 in 2010 to almost 30.000 primary hips in 2017 and primary total knee arthroplasty has increased from 20.000 to almost 30.000 implants in 7 years. These numbers underscore the importance of discriminating preoperatively which patients will benefit and who will not benefit from TJA. The latter improves not only patient care (i.e. optimise non-surgical treatment) but also reduces unnecessary surgery with subsequent unsatisfied patients and health care costs.

Baseline health factors associated with outcome of joint arthroplasty or OA disease status: frailty index, handgrip strength and molecular profiling.

Since the musculoskeletal system is a high energy-consuming organ, analysis into metabolic health of patients is important. We have assessed baseline health status in three different ways: first, by a questionnaire focussed on frailty (**Chapter 4** and **Chapter 5**), second by means of a physiological measure of muscle quality (**Chapter 6**) and third by evaluating blood metabolites in patients (**Chapter 7**).

III A Frailty

The Groningen Frailty Indicator (GFI) was developed for elderly (aged ≥ 65 years) to assess the level of frailty based on the following characteristics; mobility, cognition, perception, nutrition, poly-pharma, social status and depression. A first step to use it in end stage hip or knee OA patients was to assess the validity and feasibility in a population of over 3000 end stage OA patients on a waiting list for arthroplasty surgery. The GFI convergent and discriminatory validity in these patients was comparable to that in elderly. Using the GFI in our population showed in **Chapter 4** that about one-third of the patients undergoing THA (33%) and a quarter of the persons undergoing TKA (24%) are frail (GFI score ≥ 4).

Using the Frieds Frailty Phenotype (FFP) scoring system, Mandl *et al*[20], found that 8% of the end-stage knee OA patients experienced frailty. However, this scoring system does not include a domain on activities of daily life, which the GFI does include. Mandl *et al* did record the number of patients who report difficulties with activity of daily life, this was an additional 17%. Combining these percentages give comparable numbers of persons who experience frailty as found by our study using the GFI.

Chapter 5 demonstrated that GFI-determined frail patients scored preoperatively lower on each domain of the HOOS/KOOS as compared to the non-frail patients. However, both frail and non-frail patients improved similarly after surgery. Therefore, not the GFI but the functional level of the patient before surgery was the best predictor of functional outcomes after surgery.

Although the GFI does not preoperatively distinguish between the to be expected functional outcomes, frail THA patients did have a significantly higher reoperation rate in the year following their primary operation (6.4% in frail THA patients and 2.1% in non-frail patients, P=0.005). In TKA the reoperation rate in frail patients was also higher, albeit not statistically significant (3.7% in frail patients vs 2.1% in non-frail patients, P=0.278). The GFI may not predict functionality after surgery, it does give an indication of the success of surgery.

The importance of the pre-operative functional score as predictor for postoperative outcome raises new questions, such as 'what is the optimal timing to perform arthroplasty surgery'? The longer arthroplasty is postponed by means of pain-(pain)medication; the functional status of the patient will further decline. Currently there are no succinct guidelines for the timing of arthroplasty.[21] Optimisation of timing of surgery with respect to preoperative health status may improve outcomes.

Preoperative physiotherapy may boost the functional scores before undergoing arthroplasty surgery. Moreover, physiotherapy may change the patient's lifestyle and making him/her more prone to pursue a more active lifestyle after surgery. Although preoperative pain levels may prevent physical activity or physiotherapy, it is important to assess the patients' functional state before surgery, and prime patients to have an optimal musculoskeletal status before undergoing arthroplasty.

The fact that the GFI was not predictive for the postoperative outcome score may be due to selection bias by the orthopaedic surgeon during the preoperative period. Patients who at face value were deemed too frail by the surgeon are most probably not selected for TJA surgery and thus not included in this study. Though a surgeon does not use a frailty questionnaire, studies have shown that the 'initial clinical impression' of a physician gives a fair indication to assess the risk of mortality as well as of patient's biological age.[22,23]

III B Handgrip Strength

Although the GFI distinguished to some extend preoperatively between patients with good and less favourable outcome after TJA, a more objective clinical measure, such as handgrip strength (HGS) may be of better use (**Chapter 6**). HGS has been associated with adverse surgery outcomes and represents overall patient's strength and as such it may be a proxy for frailty.[24-26]

The HGS in end stage hip or knee OA patients (i.e. patients indicated for TJA surgery) was 34 kg for males and 20 kg for females, which is lower than the reference values of 42 kg for healthy males and 26 kg for healthy females of similar age.[27] Preoperative HGS was associated with the majority of the included outcome scores. The largest effect was seen for both THA and TKA patients for the domain '*function* *in sport and recreation*' of the HOOS/KOOS questionnaire into functional outcomes, independent of gender, age, BMI and preoperative score (THA: 0.681, P=0.005; TKA: 0.520, P=0.049). For the THA patients, also a moderate effect was found for the domain "*symptoms*" (coefficient 0.564, P=0.001) of these scores.

This study had only one pre-operative HGS measurement, no measurements were made over time in the preoperative period nor post-surgery. However, although only one measurement was available, we did find that the pre-operative HGS was associated with some specific domains of functional outcome scores. This predictive power of HGS for postoperative outcome may improve if multiple preoperative measures were available. For that matter, a decline of the HGS, determined by multiple measurements, may be a stronger predictor of frailty compared to just one measurement. Nevertheless, also one time measurements of HGS, readily applicable in clinic, will provide the orthopaedic surgeon as well as the patient information on the to be expected outcome of THA and TKA. More accurate measurements into muscle mass and muscle quality may lead to better predictions of surgery outcomes, however, the measurement of HGS is fairly simple and feasible within the current clinical practise.

III C Metabolites

Recovering after major surgery like TJA, requires a strong ability to resist stressors. A lower ability to resist stressors, i.e. frailty, is reflected by poor metabolic health. There may be metabolic profiles that may reflect the susceptibility of a person to develop OA, their progression rate and may be key in their response to joint replacement surgery. To assess whether specific baseline metabolic profiles associate to prevalent OA and may eventually predict patients' outcome in terms of progression of disease, we performed a metabolomics analysis among OA patients in both a cross-sectional and a follow-up design. Over 200 different metabolites were assessed in 1564 OA cases of whom half had radiographic progression of OA over time. Many of the metabolomics parameters are correlated, therefore a principal component analysis was used to combine the metabolites into 23 different composite scores (i.e. groups of highly correlated metabolites). These composite scores were linked to the different OA-phenotypes (hip OA, end-stage hip OA, hip OA progression, knee OA, end stage knee OA and knee OA progression), independent of age, sex, fasting status and BMI.

Three composite scores were found to be associated with both cross-sectional OA and OA progression. First, a lower level of a composite score of Histidine and Glutamine was associated with both prevalence of hip OA, end-stage hip OA and knee OA as well as with OA progression in the knee. This association has not been reported earlier.

Secondly, a composite score of fatty acid make-up was associated with end stage hip and knee OA and with progression of hip OA. This composite score consists of the fatty acid chain length, the saturated fatty acids ratio and the level of unsaturation of fatty acids. This finding is in line with observations in rats showing that long chain fatty acids induce both a metabolic syndrome as well as knee OA.[28-30]

Finally, we found a composite score of alanine, pyruvate and lactate, markers of energy metabolism, to be associated with end stage hip and knee OA and progression of hip OA. However, this association was positive in the cross-sectional analysis, but was inversely associated with progression of OA. The mechanisms of these associations are most probably driven through the energy consumption of chondrocytes, which are known to switch from oxidative phosphorylation to glycolysis in OA, provided that such a switch is in some way reflected by the metabolite profile in the circulation.[31] The inverse association for progression of hip OA, however, warrants further investigation.

This metabolomics study places composite scores of fatty acid make-up and energy balance, histidine and glutamine at the heart of the link of osteoarthritis and the metabolic syndrome. Future research should be aimed at replicating our findings, comparing them to OA markers currently used in the clinic and epidemiological studies and subsequently further elucidate the mechanisms behind these associations. Evidence for a causal link between the observed metabolites and OA may be explored by Mendelian Randomization studies in which genetic variants associated to the metabolites are tested for association with OA related endpoints.

Alternatively, metabolite levels and their relation to OA progression may be explored by intervention studies focused on histidine, fatty acid chain length and saturation. Physical exercise has well known effects on metabolic switches in the muscle and other basic aspects of ageing relevant for OA, such as cellular senescence. Such intervention studies may include also OA measures and cartilage tissue which is not regularly done.

The metabolites which were identified in **Chapter 7** may not be specific risk factors for developing OA, rather they may be markers of an overall state of vulnerability of the whole system. This vulnerable state may allow for the development of progression in chronic diseases such as OA.

The analyses presented in this thesis were all performed on previously collected data, either by performing a meta-analysis on available literature or by combining collected data from different prospective cohorts. Thus these “old” data gave a new impulse to research. The latter also stress the importance of making data collected for specific research questions available for new research questions. And to combine data from different groups to fill in the bigger picture on health related problems as well as principles on vitality.

This thesis stressed the importance of an overall integrated longitudinal study on patients, including repeated blood samples as well as patient reported outcome questionnaires, HGS and accelerometer measures as well as clinical measures at the start of the diagnosis of OA until years after their arthroplasty surgery. Such a study may identify markers that can help to distinguish patients with good and less favorable outcome and even the likelihood of adverse events after either conservative or surgical interventions, but will also give clues on preventive measures.

Conclusions

The current study is an exhaustive effort to elucidate predictors of outcome measures in surgically treated patients with end-stage osteoarthritis, ranging from patient reported outcome measures to molecular profiling. Some conclusions can be drawn:

- Metal-on-metal prostheses have an increased long-term risk of mortality (**Chapter 2**) and require close monitoring.

- Patients with hip or knee prostheses in situ adhere more often to the Dutch guideline for physical activity as compared to the general Dutch population (**Chapter 3**).

- The self-reported frailty as measured by Groningen Frailty Indicator is a valid questionnaire for end stage hip and knee osteoarthritis patients (**Chapter 4**), however, it does not have value in predicting the functional outcome of arthroplasty (**Chapter 5**).

- Frail patients have lower functional scores before arthroplasty, which may influence their functional outcome score after arthroplasty (**Chapter 5**).

- Handgrip strength is of value in predicting the outcome score on certain scales of the functional assessment questionnaire (**Chapter 6**).

- Osteoarthritis prevalence and progression is associated with certain composite scores of blood metabolites emphasizing the metabolic component in osteoarthritis (**Chapter 7**).

The future from a patients' perspective

As patients are becoming increasingly more interested in participating in the medical decision making process, the orthopedic surgeon needs tools to accurately inform patients on what to expect from surgery. The tools presented in this thesis (frailty questionnaire, handgrip strength and metabolic profiling) may give a patient and the treating orthopedic surgeon more specific individualized data which are associated with outcome. These data can be used in the complex process of pre-intervention (both conservative as well as surgical) counseling between patient and his/her orthopedic surgeon. It will improve the shared-decision-making-process, deciding whether it is best to opt for a surgical intervention or first do a serious effort for a conservative (physiotherapy / lifestyle interventions) approach to the treatment of osteoarthritis.

In the future evermore measures of the patients' general wellbeing and daily activities can be, and will be, collected; more wearables and apps are designed to monitor the patient's health, but also its shift from normality (which has to be defined).[32-34] Also, specific questionnaires which are part of cohort studies can be admitted to patients by means of apps, leading to a reduction of questions, thus saving time and costs and increase efficiency.[35]

Virtually every smartphone includes an accelerometer (e.g. pedometer), which keeps track of the number of steps, but also quality of walking (e.g. fast, slow or uphill) and heartbeat in relation to the activity. Currently, a systematic review is conducted on the use of apps in mobile devices as a measure to assess physical activity and sedentary behavior.[36] Besides monitoring, apps have also potential as motivating tools to coach individuals into a more active lifestyle. A good example of the potential of stimulating physical activity was the Pokémon-GO rage which urged sedentary people to use their musculoskeletal system.[37] The SMART-MOVE study demonstrated that besides increasing the physical activity levels of the participant, also their peers may get involved in using apps and increasing their physical activity levels.[38]

Skrepnik *et al*[39] report that the use of a smartphone app (OA GO) which is focused on increasing mobility in knee OA patients actually lead to more steps per day. Patients who were randomized to follow the application performed better on the six-minute walking test. With up to 80.2% of the patients following the program for 180 days and 67.3% of the physicians reporting to be likely or very likely to recommend the use of this application, it is a very feasible method to motivate patients with knee OA.

Besides motivating patients during the course of their disease to be physically active, prevention is an even more important issue to be addressed in earlier stages of health decline. By collecting handgrip strength measurements during lifetime, assess frailty every once in a while by means of validated assessments and check the metabolic profile of elderly regularly, the patients might be motivated to action themselves if data are presented in an accessible, understandable and comprehensive way, such as a personal story-board within an app, seems to have positive results.[40] The person, not-patient-yet, may take action and/or preventative measures when a gradual increase of vulnerability is detected, before a person gets actually sick. However, any action on presented data should be taken by persons themselves and not by an overall controlling system, human integrity of taking actions should be safeguarded.

Such long-term monitoring may prevent disease, lead to earlier detection of disease and prevent severe outcomes. Also, by having a clear overview of the patient's basic levels of resistance and vulnerability over time, the final outcomes of an intervention such as arthroplasty may be more predictable. Long term monitoring may improve health and prevent disability from chronic diseases.

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