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The role of small, non-coding RNAs (miRNAs) in the development of aseptic loosening following total hip arthroplasty

Submission date
09/03/2024

Recruitment status
No longer recruiting

Registration date
18/03/2024

Overall study status
Completed

Last Edited
11/11/2025

Condition category
Musculoskeletal Diseases

[_] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Total hip arthroplasty (THA) is one of the most effective surgical treatments of the past century. THA is implemented to treat severe hip osteoarthritis, aiming to reduce pain and enhance hip joint function. Survivorship of THA implants has improved over the years, such that approximately 80% of current implants still function optimally at 25 years postoperatively. Advances in materials, implant designs and surgical techniques have decreased the incidence of complications, however aseptic loosening, the clinical end stage of bone loss around a joint replacement or periprosthetic osteolysis (PPOL), remains the most frequent complication, accounting for at least 50% of all revision surgeries according to national registries. The purpose of this study is to identify microRNA (miRNAs; small molecules found in cells that play a role in controlling how genes work) that are up-regulated or down-regulated in patients with aseptic loosening after THA and recognise potential differences in the expression of these miRNAs between control patients undergoing THA for degenerative osteoarthritis, asymptomatic patients following primary THA and patients with confirmed aseptic loosening after primary THA. Apart from identifying new molecular pathways involved in the progression of aseptic loosening, the study will also investigate a potential protective or inductive role of some miRNAs in the process of periprosthetic osteolysis. The secondary goal is to implement the use of these miRNAs as biomarkers to evaluate the possibility for a patient to develop aseptic loosening after THA as well as possible targets for the development of new and more effective pharmaceutical treatments or even gene therapies.

Who can participate?
Patients aged 40 years old and over who are undergoing or have undergone primary THA

What does the study involve?
Patients will be divided into three groups: Group A (control), including patients undergoing THA for degenerative hip osteoarthritis, Group B including patients with no clinical or radiological findings of aseptic loosening after primary THA and Group C including patients with clinical and radiologically confirmed aseptic loosening after primary THA. Blood samples will be collected from all patients. For Group A and C patients, peripheral blood samples will be collected before

surgery while synovial membrane samples will be collected intraoperatively. Synovial membrane samples will not be collected from Group B patients since they are not candidates for any surgical intervention. Results will be analysed to identify miRNAs associated with the expression of peri-inflammatory cytokines at a post-transcription level and thus with the biochemical pathway of periprosthetic osteolysis and aseptic loosening.

What are the possible benefits and risks of participating?
Participants will not benefit from taking part in this study. However, the knowledge gained could help use some miRNAs as biomarkers to estimate the risk of developing aseptic loosening after primary THA in the future. These miRNAs could also work as treatment targets against the inflammatory process of periprosthetic osteolysis. There are no additional risks from participating in this study beyond those of having routine primary revision THA surgery.

Where is the study run from?
University Hospital of Patras (Greece).

When is the study starting and how long is it expected to run for?
March 2021 to October 2024

Who is funding the study?
University of Patras (Greece).

Who is the main contact?
Dr Papagiannis Spyridon, papajohn_1217@hotmail.com

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number

Nil known

Study information

Scientific Title
Alterations in small non-coding RNAs (miRNAs) and the potential role in the development of aseptic loosening after total hip replacement: Study protocol for a retrospective, observational, cross-sectional study

Study objectives
The primary goal is to identify miRNAs associated with the pathophysiology of aseptic loosening and indicate potential differences in the hyperexpression or hypoexpression between patients with aseptic loosening, patients with the degenerative hip disease and patients with no signs of loosening following total hip arthroplasty. The secondary goal is to use these miRNAs as biomarkers to estimate the possibility of a patient developing aseptic loosening after total hip replacement and as possible treatment targets.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 22/03/2021, Research and Ethics Committee University Hospital of Patras (Rion, Patras, 26500, Greece; +30 2613603459; achaidop@pgnp.gr), ref: 164/20.04.2021

Study design
Observational cross-sectional study

Primary study design
Observational

Study type(s)
Diagnostic, Prevention, Screening

Health condition(s) or problem(s) studied
Aseptic loosening following primary total hip replacement

Interventions
MiRNAs will be isolated, observed and compared from peripheral blood samples from control patients who are undergoing primary total hip arthroplasty (THA) due to degenerative hip osteoarthritis (group A), patients with no clinical and radiological signs of loosening following primary THA (group B) and patients with clinical and radiological signs of aseptic loosening after primary THA who are candidates for revision surgery (group C). MiRNAs will also be isolated from synovial membrane samples from Group A and Group C patients. Synovial membrane samples will not be collected from Group B patients since they are not candidates for any surgical procedure.

The study will primarily investigate (microRNA) miRNAs that are up-regulated or down-regulated in patients with aseptic loosening after THA, the differences in the expression of miRNAs among patients with hip osteoarthritis requiring surgery, asymptomatic patients after THA and patients with clinically and radiologically confirmed aseptic loosening after THA requiring revision

surgery and the potential protective or inductive role of some miRNAs in the process of periprosthetic osteolysis and aseptic loosening.

Secondary outcomes include an investigation of miRNAs as biomarkers to evaluate the possibility of a patient developing aseptic loosening after THA and as possible targets for the development of new and more effective pharmaceutical treatments or gene therapies.

A thorough medical history will be recorded for all eligible patients taking into consideration all inclusion and exclusion criteria. The exclusion or confirmation of aseptic loosening for Group B and Group C patients respectively, will be made based on clinical findings and anteroposterior and lateral hip radiographs. Patients' clinical and functional level will be assessed and documented according to the Harris Hip Score and SF-36 Score. Radiolucencies among bone-implant interface, cup migration or tilting, varus tilting and/or gross subsidence of the femoral stem and eccentric position of the femoral head in the acetabular cup indicating wearing-out of the polyethylene are all considered radiological signs of implant loosening and will be thoroughly examined in the enrollment phase. Other causes of functional limitations and pain after total hip arthroplasty such as periprosthetic fractures, dislocations, implant malposition or failure will be ruled out for Group C patients based on clinical and radiological findings. Septic loosening will also be ruled out using blood tests (Total White Blood Count) and serology tests including Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP). Intraoperative cultures will be obtained to confirm the aseptic environment of implant loosening. Blood samples will be collected from all patients. Peripheral blood samples from Group A and C patients will be collected prior to surgery while synovial membrane samples will also be collected intraoperatively. Group A patients will undergo primary total hip arthroplasty as scheduled, while Group C patients will undergo revision arthroplasty as scheduled as well. Synovial membrane samples will not be collected from Group B patients since they are not candidates for any surgical intervention. From these samples total RNA will be isolated, followed by cDNA synthesis using reverse transcription protocols (RT-PCR, Reverse Transcriptase-PCR). These cDNA samples will be analyzed using real-time quantitative PCR (RT-qPCR) and high-quality analysis after the development of suitable databases. This high-quality analysis will be performed in an Ion Torrent S5 Next Generation Sequencing platform. Results will be analyzed using a software combined with the above-mentioned platform, giving us the opportunity to identify with accuracy each biochemical pathway associated with the expression of miRNAs. Analyses will focus on the identification of miRNAs associated with the expression of peri-inflammatory cytokines in post-transcription level, thus revealing potential molecular pathways involved in the development of aseptic loosening.

Intervention Type
Other

Primary outcome(s)
Relative expression of miRNAs let-7i-5p, let-7e-5p, miR-15a-5p, miR-30a-3p, miR-130a-3p measured using real-time quantitative PCR (qRT-PCR) at baseline

Key secondary outcome(s))
There are no secondary outcome measures

Completion date
12/10/2024

Eligibility

Key inclusion criteria
1. Aged >40 years old
2. Patients undergoing primary total hip arthroplasty (THA) due to degenerative hip osteoarthritis (Group A)
3. Patients who underwent primary THA, without clinical and radiological evidence of periprosthetic osteolysis and aseptic loosening (Group B)
4. Patients undergoing revision surgery after primary THA, with clinical and radiological evidence of periprosthetic osteolysis and aseptic loosening (Group C)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
40 years

Upper age limit
99 years

Sex
All

Total final enrolment
63

Key exclusion criteria
1. Revision total hip arthroplasty (THA) surgery
2. Bilateral THA or hemiarthroplasty on the contra-lateral hip
3. Pre-existing other joint replacement
4. Inflammatory markers and intraoperative cultures indicating potential septic loosening
5. Cancer or immunodeficiency, patients receiving chemotherapy or immunosuppressive medication
6. Autoimmune diseases
7. Severe cognitive defects or psychiatric disorders
8. Inability to provide written informed consent to the study

Date of first enrolment
24/09/2021

Date of final enrolment
24/06/2024

Locations

Countries of recruitment

Greece

Study participating centre
University Hospital of Patras
Rion
Patras
Greece
26500

Sponsor information

Organisation
University of Patras

ROR
https://ror.org/017wvtq80

Funder(s)

Funder type
University/education

Funder Name
University of Patras

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
Greece

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated and analysed during the current study will be available upon request from Dr Papagiannis Spyridon, papajohn_1217@hotmail.com. All de-identified/anonymised data will become available after the publication of the study results. This is already included in the patient consent form.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		28/10/2025	11/11/2025	Yes	No
Protocol article		23/10/2024	03/12/2024	Yes	No
Statistical Analysis Plan			18/03/2024	No	No