ISRCTN12180483 https://doi.org/10.1186/ISRCTN12180483

Probiotics in Paget's disease

Submission date 25/01/2023	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 03/02/2023	**Overall study status** Ongoing	
Last Edited 05/12/2024	**Condition category** Musculoskeletal Diseases	

Plain English summary of protocol

Background and study aims
Epidemiological studies have shown that environmental factors influence the occurrence and severity of Paget's disease of bone (PDB), but the identity of these factors is unclear. There is previous evidence that dietary calcium and vitamin D deficiency might predispose to PDB. The study will investigate the role of dietary calcium and vitamin D and of the microbiome as environmental factors which may modify the disease activity in PDB. The aim of this study will be to explore the effects of dietary calcium and vitamin D supplements and probiotic supplements on biochemical markers of metabolic activity in patients with mild PDB who are not considered to require treatment with bisphosphonate therapy and to study effects on pain and quality of life.

Who can participate?
Adult patients with PDB

What does the study involve?
The study involves three hospital visits at baseline, 3 months and 6 months. Participants will be allocated to a treatment group and will receive either probiotics, combined vitamin D and calcium supplements, or a placebo. Participants will give a blood sample and a stool sample at each visit and will answer questions related to their quality of life and the presence of pain.

What are the possible benefits and risks of participating?
There are no benefits to taking part in this study, but the results from this study might help to improve understanding of the causes of PDB and help in the search for new treatments. It is unlikely that taking the supplements will cause any side effects, but we will be monitoring all participants closely for any adverse effects that might occur.

Where is the study run from?
The Bone research group at the Institute of Genetics and Cancer, The University of Edinburgh (UK)

When is the study starting and how long is it expected to run for?
February 2022 to January 2026

Who is funding the study?
H2020 Excellent Science - European Research Council

Who is the main contact?
Kathryn Berg, kathryn.berg@ed.ac.uk

Contact information

Type(s)
Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
303256

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
AC21099, IRAS 303256

Study information

Scientific Title
Measuring the effect of probiotics or calcium/vitamin D supplements in patients with Paget's disease of bone

Acronym
PRiP

Study objectives
A reduction of serum alkaline phosphatase will be observed in at least one of the active groups who are receiving a probiotic intervention plus calcium and vitamin D supplementation but not the control group who are receiving probiotics alone.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 05/08/2022, West of Scotland Research Ethics Service (Ground Floor Ward 11, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, UK; +44 (0)141 314 0212; WoSREC3@ggc.scot.nhs.uk), ref: 22/WS/0075

Study design
Multicentre interventional blinded randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Paget's disease of bone

Interventions
One arm of the study will receive a probiotic intervention. Probiotics have previously been evidenced to be beneficial to bone health. The probiotic intervention will consist of three lactobacillus strains in capsular form, to be taken once daily to provide 1 x 1010 PFU of lactobacillus per day. The preparation will be supplied by Probi (www.probi.com) and is identical to a supplement previously used in the prevention of postmenopausal bone loss in women. Participants will receive a three-month supply face-to-face at the baseline and 3-month visits and these will be dispensed by a qualified member of the local research team who will be familiar with the pharmacy manual. The probiotic capsules will be shipped by Probi under temperature-controlled conditions (4-8oc) to the coordinating centre where they will be stored in a dedicated temperature-controlled refrigerator. The product will be shipped from the co-ordinating centre to study centres on an intermittent basis under temperature-controlled conditions (4-8oc) and stored in local study centres in a temperature-controlled refrigerator.

Another arm of the study will receive a combined vitamin D/calcium supplement. Both are commonly used in this patient group and are known to positively influence bone health. The supplement will be provided containing 500 mg of elemental calcium and 200 units of vitamin D taken twice daily in the form of supplements purchased from Simply Supplements. Participants will receive a three-month supply face-to-face at the baseline and 3-month visits and these will be dispensed by a qualified member of the local research team who will be familiar with the pharmacy manual. The supplements will be stored at the co-ordinating centre in a locked cabinet dedicated to the study and shipped at ambient temperature to the study centres on an intermittent basis where they will be stored at ambient temperature.

The placebo arm will receive capsules containing excipients alone (maize starch) which will also be supplied by Probi and will be taken once daily. Participants will receive a three-month supply face-to-face at the baseline and 3-month visits and these will be dispensed by a qualified member of the local research team who will be familiar with the pharmacy manual. The placebo intervention will be shipped by Probi under temperature-controlled conditions (4-8oc) to the co-ordinating centre where it will be stored in a dedicated temperature-controlled refrigerator. The product will be shipped from the co-ordinating centre to study centres on an intermittent basis under temperature-controlled conditions (4-8oc) and stored in local study centres in a temperature-controlled refrigerator.

Participants will be randomised using the randomisation function on REDCap which has been programmed to allocate participants to each treatment arm to ensure an even spread of interventions within each centre.

Intervention Type
Supplement

Primary outcome(s)
Metabolic activity of Paget's disease of the bone assessed by serum concentrations of total alkaline phosphatase measured using an alkaline phosphatase test at 6 months

Key secondary outcome(s))
1. Biochemical markers of bone metabolism levels, including PINP, CTX, PTH and 25(OH)D, measured using blood samples collected at baseline, 3 and 6 months
2. Health-related quality of life measured using the 36-Item Short Form Survey (SF-36) at 6 months
3. Presence and severity of pain at sites affected by Paget's disease of the bone measured using a Visual Analogue Scale at baseline, 3 and 6 months
4. Microbiome measured using 16S sequence analysis of stool samples at 3 and 6 months

Completion date
31/01/2026

Eligibility

Key inclusion criteria
1. Aged 18 years old and over
2. Clinical diagnosis of Paget's disease of the bone confirmed by characteristic appearances on radionuclide bone scan and /or x-ray
3. Serum total alkaline phosphatase elevated above the upper limit of normal or within the upper half of the local reference range
4. Willing and able to give informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria

1. Unable or unwilling to give informed consent
2. Bisphosphonate therapy thought to be indicated for the treatment of Paget's disease of the bone on clinical grounds
3. Currently being treated with bisphosphonates, denosumab or calcitonin for any reason
4. Currently being treated with combined calcium and vitamin D supplements
5. Treatment with oral or intravenous bisphosphonates during the previous 24 months
6. Treatment with denosumab during the past 12 months
7. Treatment with calcitonin during the previous 3 months.
8. Treatment with combined calcium and vitamin D supplements during the past 4 weeks
9. Receiving probiotics during the previous 3 months

Date of first enrolment
16/02/2024

Date of final enrolment
31/07/2025

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
Western General Hospital
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Study participating centre
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Study participating centre

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Study participating centre
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TS4 3BW

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Study participating centre
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Freeman Hospital
Freeman Road
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Newcastle upon Tyne
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NE7 7DN

Study participating centre
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Stott Lane

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Study participating centre
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Study participating centre
Royal National Orthopaedic Hospital
Brockley Hill
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Sponsor information

Organisation
Accord (United Kingdom)

ROR
https://ror.org/01x6s1m65

Funder(s)

Funder type
Government

Funder Name
H2020 European Research Council

Alternative Name(s)
H2020 Excellent Science - European Research Council, European Research Council, EXCELLENT SCIENCE - European Research Council, H2020 Ciencia Excelente - Consejo Europeo de Investigación (CEI), CIENCIA EXCELENTE - Consejo Europeo de Investigación, H2020 Wissenschaftsexzellenz - Für das Einzelziel 'Europäischer Forschungsrat (ERC)',

WISSENSCHAFTSEXZELLENZ - Für das Einzelziel 'Europäischer Forschungsrat, H2020 Excellence Scientifique - Conseil européen de la recherche (CER), EXCELLENCE SCIENTIFIQUE - Conseil européen de la recherche, ECCELLENZA SCIENTIFICA - Consiglio europeo della ricerca, H2020 Eccellenza Scientifica - Consiglio europeo della ricerca (CER), ERC, CEI, CER

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to the rare nature of this disease and therefore the risk that a participant could be identified. Participant-level data will be held on secure servers at the Institute of Genetics and Cancer at the University of Edinburgh and will not be shared.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 6	12/03/2024	15/04/2024	No	No