**Robert Meertens**

**College of Radiographers Doctoral Fellowship 003**

**£24,974 awarded**

**Title:** The use of near infrared spectroscopy as a diagnostic tool to measure the haemodynamics of the microvascular blood supply to bone

## Principle Aim

To investigate the potential of near infrared spectroscopy (NIRS) as a diagnostic tool in the measurement of the haemodynamics of microvascular blood supply in bone, including bone tissue oxygenation and markers indicative of blood perfusion and blood volume in bone.

## Objectives

To gauge the existing knowledge base on the use of NIRS at measuring markers of microvascular blood supply to bone.

To determine if NIRS:

- can measure the haemodynamics exclusively in bone;

- is accurate when measuring the haemodynamics of bone;

- measurements of bone are reproducible and precise across different operators;

- measurements of bone are reproducible and precise across different participants;
- measurements are tolerable for participants; and,

- can be optimised in terms of protocols for clinical use.

To investigate the performance of NIRS against a test that also measures markers of microvascular blood perfusion and blood volume to bone: dynamic contrast enhanced magnetic resonance imaging. In the process we aim to observe any significant difference in bone haemodynamics between matched participants with and without type 2 diabetes mellitus (T2DM).

## Outcomes

If successful, further studies investigating the accurate use of NIRS in more diverse populations would be justified. This could lead to cheap, quick and tolerable methods of measuring blood supply in bone, opening new avenues of research into bone diseases involving vascular causes.

Depending on results, further research involving people with T2DM may be justified, investigating if NIRS can improve outcomes by identifying those "at-risk" of low impact fractures sooner than current methods. With an increased understanding of this disease process, alternative prevention and treatment strategies could also be developed for a population that currently has no proven effective options.

## Review of literature and identification of current gap in knowledge

Haemodynamic measurements of the microvascular blood supply to any organ or tissue can provide invaluable diagnostic information on disease processes with a vascular component. Common examples include blood perfusion imaging to assess stroke in the brain and myocardial perfusion imaging to assess viability of the diseased left ventricle [1, 2].

Microvascular blood supply measurements can include oxygen saturation in tissue (an indicator of general tissue health), blood perfusion rates to tissue (an indicator of metabolism and/or microvascular function) and blood volume measurements (an indicator of blood demand to tissue and tissue vascularity). It is important to keep these measures in context. For example, blood may be perfusing well but could be low in oxygenation, or blood may be well oxygenated but tissue is receiving an inadequate blood volume [3].

Bone is a dynamic and highly vascular tissue type that is constantly self-regulating. However because of its density and high mineral content, its microvascular supply is notoriously difficult to image using existing modalities [4]. Imaging protocols for measuring bone haemodynamics involve nuclear medicine scans, positron emission tomography (PET) or magnetic resonance imaging (MRI). These tests are expensive, have limited clinical access, involve injections, and don't allow easily repeated measurements over time [5, 6]. In addition, oxygen saturations in bone tissue cannot be measured and therefore neither can oxygen consumption

metabolism [7]. These modalities measure markers of gross perfusion and blood volume to tissue based on rates of radiopharmaceutical or gadolinium contrast uptake [8, 9]. The gold standard to measure bone oxygenation at a specific anatomical site is bone biopsy, which is invasive and painful for the patient [10].

Near infrared spectroscopy (NIRS) is a potential diagnostic solution. NIRS is non-invasive, non-destructive and non-ionising. As a diagnostic tool it is relatively inexpensive and convenient for repeat measurements or for continual monitoring of tissue in real time [11]. It can measure oxygen saturation as well as markers of gross blood perfusion and blood volume to tissue [12]. NIRS utilises similar technology to a pulse oximeter, but involves transmitting and receiving designated optical frequencies using non-invasive probes at an anatomical sight. NIRS takes advantage of the difference in absorption characteristics of oxygenated and deoxygenated haemoglobin to record markers of bone haemodynamics in real time [13]. Although near infrared light is not very penetrating in human tissue, NIRS has been shown to be able to record data through bone to depths of 4 to 5cms [14].

Presently, NIRS has gained clinical acceptance in applications ranging from diagnosis of breast lesions based on microvascular characteristics, use in functional brain studies and longitudinal brain monitoring [3]. However NIRS in not yet clinically accepted for measuring bone haemodynamics despite research in this field. This project will aim to build on existing research, investigating this application of NIRS using processes of development, feasibility testing and evaluation in line with the Medical Research Council's *"Developing and evaluating complex interventions"* framework, including validation against one of the aforementioned current diagnostic imaging techniques [15].

One of the earliest reported uses of NIRS to measure bone haemodynamics was in 2002, where NIRS was used to monitor the haemodynamics of tibial bone marrow on astronauts in a microgravity environment, as astronauts are prone to rapid bone density loss in space with non-weightbearing [5]. An associated study showed a reduction in reperfusion rates of the tibia post induced ischemia that increases with age [16].

In 2004, Pifferi et al. reported using NIRS to measure oxy and deoxygenated haemoglobin in the calcaneus [6]. Interestingly, this article also reports successful measurements of bone mineral and lipid content using more advanced "broad frequency time resolved NIRS" technology, showing expected changes across female participants aged 26-82. With advances on this technology's feasibility, this

may be another potential future application of NIRS, providing an alternative to the current gold standard for bone mineral density (BMD) measurements, Dual Energy X-ray Absorptiometry (DXA).

Several studies have reported using NIRS to measure haemodynamics of the patella, including also validating the technique using *in vitro* studies [11, 12]. Aziz et al. has also validated the measurement of oxy and deoxygenated haemoglobin involving induced vascular occlusion at the tibia using NIRS [14]. Naslund et al. has demonstrated a diagnostic application of NIRS, where blood perfusion reduction to the patella due to knee flexion were shown to be more marked in people who suffer from Patellofemoral Pain Syndrome [17]. Blood perfusion changes to the patella were also shown to be dependent on muscular contractions of the quadriceps muscle group [18].

NIRS has been used clinically to monitor haemodynamic changes in the tibia of paraplegic patients in keeping with the known changes to tibial bone structure and reduced BMD in paraplegic people following the associated reduced weightbearing activity [13]. Farzam et al. also investigated using NIRS to measure oxygenation and haemodynamics in the manubrium as a potential diagnostic tool in the early detection of blood cell proliferation associated with haematological malignancies [19]. Other research suggests a future role for NIRS as a potential diagnostic tool in cases of poor fracture healing (non-union) and arthritis [4, 20].

One particular application of NIRS is also of interest to the research team. This is the potential of NIRS for assessing bone health in people with type 2 diabetes mellitus (T2DM) [21]. Even when accounting for the known increased risk of falls, this population is at risk of low impact “fragility” fractures, despite the raised body mass index associated with T2DM being protective of BMD [22]. The association of T2DM with systemic peripheral microvascular disease raises the question if poor microvascular blood supply to bone reduces bone metabolism and bone strength, predisposing people with T2DM to fracture, independent of BMD [22]. Given the increasing incidence of T2DM in an ageing population, and the associated mortality and morbidity of fragility fracture, NIRS could play an important role in understanding this under researched mechanism of disease, informing better preventative treatment options and improving early prediction of those “at-risk” of fragility fracture in this sub-population.

## Methodology

Our primary aim is to investigate the potential of NIRS as a diagnostic tool in the measurement of haemodynamics of microvascular blood supply in bone, including bone tissue oxygenation and markers indicative of blood perfusion and blood volume in bone.

This will involve a three stage approach:

1) A systematic review of the diagnostic test accuracy of NIRS when measuring haemodynamic markers in bone in order to gauge the existing knowledge base and to guide feasibility studies.

2) Feasibility studies to demonstrate if our NIRS equipment can be used in an accurate, precise and reproducible way for measuring bone haemodynamics. This will include reference to the previously identified literature base. Feasibility studies will investigate inter-operator and intra-operator reliability of NIRS across different participants and operators, and if successful, will involve development of protocols for the clinical use of NIRS, ensuring acceptability with participants.

3) Validity studies of NIRS technology against dynamic contrast enhanced MRI imaging (DCE-MRI) to assess correlation between NIRS measurements and a known imaging test that measures markers of gross perfusion and blood volume in bone. In the process we aim to observe any significant difference in bone haemodynamics between matched participants with and without T2DM.

## Potential impact

Successful validation of NIRS could lead to further research in larger populations to investigate effective, safe and tolerable methods of measuring bone haemodynamics. This could open new avenues to under-researched bone pathologies involving microvascular mechanisms such as fracture healing, arthritis or haematopoietic malignancies. Significant results in stage 3 of this study could justify larger prospective longitudinal studies investigating the ability of NIRS to predict the risk of fragility fracture in people with T2DM, independent of BMD. Increased understanding of disease process in bone associated with T2DM could lead to the development of better preventative and curative options for T2DM populations.

## Dissemination Strategy

As well as being presented in a PhD thesis, all three stages of the project will result in presentation at conferences, practical demonstrations of NIRS, and/or published articles in peer reviewed open access journals surrounding biomedical imaging and medical imaging, including *Radiography*. Indeed, a literature review on the potential clinical application of NIRS in T2DM populations is currently in press with the *Journal of Endocrinology and Metabolism* [22].

Through academic supervisor Karen Knapp, potential positive results of NIRS can be directly presented to UK advisory boards that set clinical guidelines for the diagnosis of osteoporosis and prevention of fragility fractures.

Assuming successful validation of NIRS, dissemination will target alternative patient populations for potential diagnostic or monitoring applications, including those suffering from arthritis, haematological malignancies, paediatric metabolic bone diseases or spinal injury patients. Presentation of results will also be delivered to volunteers and service user groups involved.

## References


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