The use of near-infrared systems for investigations of haemodynamics in human *in vivo* bone tissue: A systematic review

Running Title: NIR for haemodynamic bone measurements.

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Abstract:

A range of technologies using near infrared (NIR) light have shown promise at providing real time measurements of haemodynamic markers in bone tissue *in vivo,* an exciting prospect given existing difficulties in measuring haemodynamics in bone tissue. This systematic review aimed to evaluate the evidence for this potential use of NIR systems, establishing their potential as a research tool in this field. Major electronic databases including MEDLINE and EMBASE were searched using pre-planned search strategies with broad scope for any *in vivo* use of NIR technologies in human bone tissue. Following identification of studies by title and abstract screening, full text inclusion was determined by double blind assessment using predefined criteria. Full text studies for inclusion were data extracted using a predesigned proforma and quality assessed. Narrative synthesis was appropriate given the wide heterogeneity of included studies. Eighty eight full text studies fulfilled the inclusion criteria, 57 addressing laser Doppler flowmetry (56 intra-operatively), 21 near infrared spectroscopy and 10 photoplethysmography. The heterogeneity of the methodologies included differing haemodynamic markers, measurement protocols, anatomical locations and research applications, making meaningful direct comparisons impossible. Further, studies were often limited by small sample sizes with potential selection biases, detection biases, and wide variability in results between participants. Despite promising potential in the use of NIR light to interrogate bone circulation, the application of NIR systems in bone requires rigorous assessment of the reproducibility of potential haemodynamic markers and further validation of these markers against alternative physiologically relevant reference standards.

Keywords:

Bone; haemodynamics; near infrared; emerging technologies; optical systems.

Introduction

Bone is a dynamic and vascular tissue, dependent on this perfusion to meet its metabolic demands. However, measuring the haemodynamics of the osseous vasculature is difficult with existing imaging modalities due to the high density and mineral content of bone. Imaging protocols typically involve nuclear medicine scans, positron emission tomography (PET) or contrast enhanced magnetic resonance imaging (MRI) which are expensive, have limited clinical access, involve injections and do not readily allow longitudinal evaluation. In addition, these techniques do not allow evaluation of oxygen saturation within the tissue, as these modalities can only measure markers of gross perfusion and blood volume based on rates of radiopharmaceutical or gadolinium contrast uptake [1].

Near infrared (NIR) optical systems are a potential solution. They have the advantages of being non-invasive, non-destructive, non-ionising, inexpensive and allowing repeat or continuous measurements. NIR optical systems involve transmitting and receiving designated optical wavelengths using probes at an anatomical site. These systems take advantage of the difference in absorption characteristics of oxygenated and deoxygenated haemoglobin to record markers of bone haemodynamics in real time including tissue oxygenation, perfusion, blood flux and blood volume [2]. Although NIR light only penetrates human tissue superficially, systems have been shown to be able to record data non-invasively through *in vivo* tissue to depths of up to 4 cm [3].

NIR optical systems are already established research tools in muscle physiology and transcranial cerebral circulation [4, 5]. The use of transcranial NIR optical systems, demonstrates that NIR light can penetrate bone tissue, and raises the possibility of its use in assessing bone haemodynamics. Development of NIR optical systems could benefit research in a range of bone pathologies with suspected vascular components, such as the earlier

detection, prevention and monitoring of haematopoietic malignancies, osteoporosis, non-osteoporotic fragility fractures, slow fracture healing and forms of arthritis. The primary aim of this systematic review is to gauge the existing knowledge base on the ability of NIR optical systems to measure haemodynamic markers of blood supply in bone tissue, and to establish their potential as a research tool in this field.

Methods

An initial scoping review suggests no previous systematic review on this topic has been performed, therefore a diverse but relatively small evidence base was expected. As such broad search criterion were established for studies investigating *in vivo* bone tissue at any anatomical bony site in human participants. Studies using NIR optical systems in either healthy or diseased human populations (or both) were considered eligible. Any optical system utilising NIR wavelengths (600-1050 nm) using a haemodynamic marker that could give insight into the haemodynamic state of the bone tissue sampled was considered eligible. This could include systems measuring haemodynamic markers of blood flux, oxygen saturation, oxygenated or deoxygenated haemoglobin concentration changes or blood volume. Any indication for utilising the NIR optical systems was eligible, including validation for a particular application, diagnosis of disease states, prognostic assessment, longitudinal monitoring or screening purposes.

Given the broad scope of the review, a wide range of reference standards were eligible, such as bone biopsy for measuring oxygenation of bone tissue; MRI, nuclear medicine or angiographic protocols for measuring bone perfusion; or, direct clinical observation of tissue perfusion intra operatively. Again, allowing for broad search criterion, a comparator test or external reference standard for results was desirable, but not essential for study eligibility. There were no restrictions on the geographical location or year of publication for studies, but

only studies published in English were eligible. Case studies of individual participants were excluded, as were opinion pieces, reviews and editorials.

Search Strategy

Pre-planned search strategies using medical subject headings and keywords were developed around key inclusion criteria for searches using MEDLINE and EMBASE online databases. Grey literature databases including conference abstracts, theses, and unpublished works were searched, including Web of Science, Proquest, OpenSIGLE, OpenGrey, and the British Library EThOS database. At this point the reference list and further citations of any eligible studies were hand searched. Authors were contacted where clarification or full text access was required. All searching was carried out by the primary author who then removed duplicates and screened the returned results based on title and abstract. The remaining studies were considered for inclusion based on a blinded full text assessment by two independent reviewers (RM and FC). Upon agreement of eligible studies, the primary author independently extracted relevant key data using a pre-piloted data extraction proforma (extracted data is presented in Supplementary Materials 1). Searches were performed in September 2015, with a repeated addendum search of MEDLINE and EMBASE performed prior to publication.

Assessment of Risk of Bias

Identified studies were also scrutinised by the primary author across 6 domains of potential intrinsic biases using the Cochrane based Risk of Bias Assessment Tool for Non-randomised Studies (RoBANS) tool to form an overall judgement of reporting quality as either "good", "fair" or "poor" [6]. External applicability and generalisability of studies was also assessed using these categorical criterion. Methodological patterns or trends for "unclear" or "high" areas of risk of bias were identified and their potential effects are discussed in context within

the narrative synthesis of the review (extended assessment results are presented in Supplementary Materials 2).

Data Synthesis

Due to the clinical and methodological heterogeneity of the identified studies, statistical synthesis via meta-analysis was not appropriate. As such, narrative synthesis of identified studies has been performed primarily synthesised around the NIR optical systems of interest and grouped around the anatomical locations or target conditions investigated. Discussion is also in context of the haemodynamic markers employed, types of participants, and comparators. The review also includes discussion on the strength of the evidence accumulated including consideration of the risk of bias of individual studies, patterns in biases, the consistency of results across studies, the applicability of results across the general population, as well as the strengths and limitations of the review process. Further detail on the protocol for the review are registered on the PROSPERO database [7].

Results

Overview of Findings

A summary of search results and data extraction is presented in Figure 1 and Supplementary Materials 1. Eighty eight studies were included for full text analysis. These were predominately peer reviewed journal articles along with 5 conference proceedings [8-12] and 2 theses [13, 14]. Study publication dates ranged from 1987 to 2017 and there was wide geographical variation with publications based in 13 different countries.

Twenty one studies were identified using near infrared spectroscopy (NIRS) [3, 8, 11, 13, 15-30] and 10 studies were identified using photoplethysmography (PPG) non-invasively on *in vivo* bone tissue [10, 24, 31-38]. Fifty seven studies were identified using laser Doppler flowmetry (LDF) *in vivo* [9, 12, 14, 39-94] of which 56 were intra operative. Only one study

using LDF attempted to measure bone non-invasively [92]. Most studies were in adult populations with only 7 of the 56 LDF studies including paediatric populations [41, 46, 70-72, 78, 91].

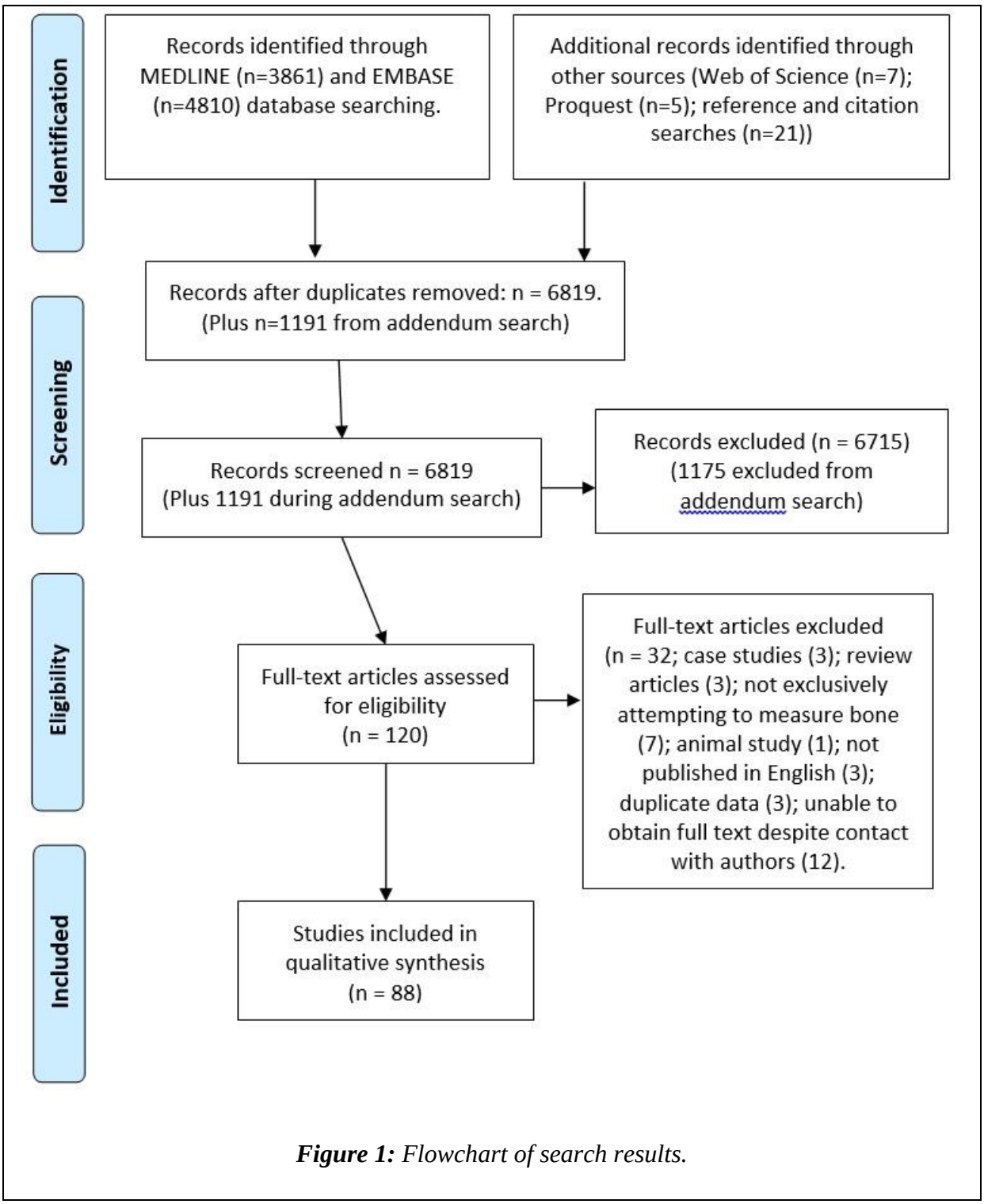

Figure 1: *Flowchart of search results.*

System Characteristics

Near Infrared Spectroscopy (NIRS)

Studies most commonly utilised "continuous wave" NIRS systems using spatially resolved or modified Beer-Lambert law algorithms. These systems utilise at least 2 or 3 discrete wavelengths of NIR light in the first NIR window (600 nm-1200 nm) to detect changes in oxygenated and deoxygenated haemoglobin concentrations by taking advantage of their different attenuation properties. This also allows these systems to measure oxygen saturation and total haemoglobin concentration changes in the tissue sampled. The oxygen saturation is the mean saturation across the arterioles, capillaries and venules. All were using reflectance spectroscopy (light scattered back from tissue) apart from transmission spectroscopy (light scattered through tissue) studies looking at the calcaneus [8, 22, 30] and mandible [21, 23]. For reflectance spectroscopy, probe spacing (affecting the depth of tissue measured) varied from 10 mm [13, 19, 25], 20 mm [13], 25 mm [8, 20], 30 mm [15-18, 26], and 40 mm [3, 18]. Temporal resolution typically ranged from 1 second [17] to 12 seconds [20, 30].

Use of time resolved spectroscopy systems are reported in five studies [8, 20, 22, 29, 30]. These allow measurements of absorption and scattering coefficients for bone tissue and therefore absolute concentrations of oxygenated and deoxygenated haemoglobin are calculated with participants at rest (in μM) [8, 19, 20, 22, 23]. Farzam et al. 2013 also reports on use of a frequency domain based NIRS system utilising 15 NIR laser sources (5 each at 3 different wavelengths) based around 2 photomultiplier detectors [19].

Six studies used NIRS systems utilising a broadband spectrum of NIR light enabling the system to calculate absolute concentrations of haemoglobin and in some cases also water, collagen, mineral and lipid content in the bone tissues sampled [8, 20, 22, 23, 28-30].

Additionally, four studies also measured markers of blood flow rates utilising emerging diffuse correlation spectroscopy technology [8, 20, 27, 30].

Photoplethysmography (PPG)

We identified 10 PPG studies from two research groups investigating the patella and tibia [10, 24, 31-38]. These studies utilised bespoke PPG systems making use of an isobestic 804 nm NIR wavelength to measure the amplitude of pulsatile flow in bone tissue based on attenuation changes in reflected signal. When reported, inter-probe spacing ranged from 15-25 mm. Some studies also measured overlying skin tissue, utilising a less penetrative wavelength in the visible range (either 526 nm or 560 nm). All studies used "peak to peak" amplitude during pulsatile flow as their primary outcome measure, typically measured and averaged over a 30-60 second period to gain a mean value representing the strength of pulsatile flow. Changes were then typically compared to baseline measurements during and/or after an intervention in either relative (i.e. percentage change) or absolute terms (in Volts).

Laser Doppler Flowmetry (LDF)

Most studies reported the use of a commercial LDF system utilising a monochromatic wavelength typically at 632 nm, 780 nm, 785 nm, or 830 nm. LDF systems derive a measure of flowmetry from the Doppler frequency shift induced by the moving red blood cells. Changes in the frequency power spectrum of the reflected light provide a measure of the concentration of moving red blood cells (blood flux or flowmetry) in arbitrary units (described as perfusion units, flux units, or detector signal measured in milliVolts). A mean amplitude of pulsatile flow is calculated over a set period (typically 60s or less). Comparison of these values across participants should be done cautiously, and typically these values are

used to assess relative changes following a vascular challenge (either expressed as absolute change or relative percentage change).

LDF systems only measure to a depth typically less than 4 mm [95], and therefore 56 of 57 studies involve intra operative use of LDF with probe placement directly on bone or intra-osseous measurements. Two studies utilised laser speckle techniques involving laser light interference from a tissue surface and mapping blood flux to produce a 2D flowgraphy "heat" map. These were used intra-operatively to study the flux in the surface of the bone tissue up to a depth of 2mm, namely the femoral head [50] and the cochlea promontory [73].

Study Characteristics

Studies looking to investigate bone tissue non-invasively used a wide range of superficial anatomical bone sites including the tibia, calcaneus, radius, ulna, greater trochanter of the femur, patella, mandible and manubrium/sternum. In addition, invasive LDF procedures also investigated deeper bone tissue including the proximal femur, acetabulum, cochlea, maxilla, metatarsal, humerus and lumbar vertebrae. Studies could broadly be split into two categories. Firstly, studies investigating the feasibility of NIR technologies for measuring bone tissue in healthy adults. Secondly, studies that used previous evidence to defend the validation of NIR technologies, and applied these systems for a physiological research purpose.

Feasibility Studies

The most substantial work demonstrating NIRS and PPG could truly measure haemodynamic parameters of bone tissue non-invasively was based around studies that demonstrated significantly lower oxygen extraction rates and reperfusion rates in bone tissue compared to adjacent muscle tissue. These two parameters were derived during and after extended arterial occlusions of the leg respectively, reflecting bone's lower metabolic rate compared to muscle [11, 15, 16, 19, 26]. Three studies demonstrate a non-significant confounding contribution of

superficial tissue to PPG and NIRS measurements of the patella and tibia by selectively altering superficial tissue haemodynamics either through the localised introduction of vasodilating or vasoconstricting elements such as gentle compression [32], cold packs [13], nitro-glycerine patches [32] and liniment [34]. However, Klasing et al. 2003 does report a systematic influence from superficial tissue on NIRS measurements, although it is noted this is a much earlier study [26].

Binzoni et al. 2013 was the only study focusing purely on non-invasive LDF measurements in bone through the skin surface. Feasibility work was undertaken in healthy participants with a source/detector spacing of 1.5 cm giving enough penetrative depth to measure superficial bone *in vivo* at four anatomical sites [92]. Diffuse correlation spectroscopy technology with NIRS also provides blood flux information non-invasively but at greater tissue depths and may supersede LDF here given the added advantages of NIRS systems [30].

Other applications of NIRS and PPG systems applied to healthy populations included haemodynamic measurements taken during positional changes such as leg extension, or head up/down tilt to demonstrate oxygen saturation and blood volume changes [10, 13, 17, 24, 37, 38]. Four studies examined the effects of positive and negative external pressure changes using lower body pressure chambers on the amplitude of PPG pulsatile flow and oxygen saturation [24, 31, 33, 38]. In the case of Larsson et al. 2014, the use of hyperbaric chambers and variable respired oxygen levels were also used to observe their effects on bone haemodynamics at the patella [31]. These studies concluded that the use of pressure alterations may have applications for therapy by mimicking weight-bearing physiology in a microgravity environment, or for potential therapeutic applications involving vascular mechanisms in bone. Three studies investigated the effects of exercise on tibia and patella haemodynamics using exercise bikes [13], rowing machines [13, 28] or high intensity

quadriceps workloads [36]. For time resolved NIRS systems, absolute measurements could be taken on healthy adult participants simply at rest [8, 20, 22, 29, 30].

Physiology Research Applications

Studies using NIR optical systems for physiological research in diseased populations were predominately LDF studies, focusing on dynamic flux changes in response to fixed stimuli or during various stages of a surgical intervention. Some studies used case-control designs to correlate these results with other clinically relevant observations assessing the predictive role of intra-operative LDF on outcomes.

The proximal femur and hip joint represented one of the biggest areas of interest for research involving LDF in bone tissue, with 19 studies [9, 39, 41-44, 48-50, 54, 58, 65-67, 76, 77, 82, 84, 91] found investigating a range of clinical applications including osteonecrosis (either idiopathic, steroid induced, or following neck of femur fracture) [50, 65, 82, 84], approaches to hip resurfacing arthroplasty [9, 39, 42, 67, 77] or total hip replacement following arthritis [44, 48, 49, 58, 66, 82], femur-acetabular impingement [43], hip joint debridement [76], and congenital developmental problems [41, 54, 91]. Specifically most studies took measurements from the femoral head and neck, but others also looked at intra-trochanteric regions [65, 84], the greater trochanter [48, 58, 66], proximal femoral shaft [58], medial calcar [58], or acetabulum [49, 54].

There were 6 studies identified that used LDF intraoperatively to investigate patellar blood flux changes before and after positional changes or different surgical manoeuvres in adult patients having total knee arthroplasty [52, 55, 57, 61, 74, 81]. Five studies used LDF technology to measure blood flux in the manubrium [40] or sternum [51, 59, 60, 75] during and following open cardiac surgery involving the internal mammary arteries. Seven studies looked at the use of LDF to measure blood flux in the mandible [14, 62, 88], maxilla [90, 93,

94] or both [63, 89] for patients undergoing maxilla-facial or dental surgery including wisdom tooth removal [14], dental implants [62, 88, 94], osteomyelitis [89] or corrective maxillary surgery [63, 90, 93]. Eleven studies reported on the use of LDF to assess blood flow in the bony wall of the cochlea [45, 46, 68-73, 79, 80, 87] to investigate a range of inner ear pathologies including otosclerosis [73, 80], Meniere's disease [79], curative treatment for uncontrolled drooling [68, 69] or idiopathic or congenital hearing loss and surgical implantation of hearing aid devices [46, 70-72]. Four studies from the same group investigated the use of LDF technology for assessing bone perfusion during the surgical debridement of bone tissue in adult patients compromised by acute trauma (such as open fracture) and/or osseous infections such as osteomyelitis [47, 83, 85, 86].

LDF has also been used to investigate successful post-operative monitoring of fibular bone grafts [78]; intra-osseous haemodynamic measurements of thoracic and lumbar vertebral bodies during mimicked unilateral and bilateral ligation [53]; for investigating the predictive ability of humeral head fracture patterns for determining the risk of humeral ischemia [56]; and for investigating the blood flux in the first metatarsal head during corrective surgery [12, 64].

The clinical utility of NIRS has been explored in the mandible [18, 21, 23] and sternum [25]. In a case-control manner, mandibular conditions such as osteoradionecrosis post radiotherapy [21, 23], and fibular grafting post tumour removal [18], as well as chest wall measurements taken post cardiac surgery [25] were explored. Results showed potential for the use of NIRS for post-operative monitoring using oxygen saturation measurements, however the small sample sizes and shortage of adverse outcomes precluded the ability to identify a diagnostic predictive threshold.

Naslund et al., 2007 used PPG to investigate haemodynamic differences between cases of Patello-Femoral Pain Syndrome with age, gender and body mass index (BMI) matched controls. This study demonstrated cases of Patello-Femoral Pain Syndrome had significantly reduced PPG pulsatile amplitude when flexing their affected knee to 90 degrees for 5 minutes, supporting the hypothesised ischaemic element to pathogenesis [35].

Reliability of NIR systems

Broadly speaking, study results were predictive of the expected haemodynamic changes during interventions. However, across most studies wide variability in results between participants was evident, especially across applications of LDF. Crucially, no studies were identified specifically addressing the reliability or reproducibility of NIR optical systems. Studies that did attempt to assess reliability typically did this in a superficial or *ad hoc way* in small samples without statistical analysis of agreement or reliability. Approaches included comparing contralateral results, analysing repeat measurements for their variability (either in the same or different sessions), or simple comparison of results with existing literature in animal studies or involving different tissue types.

This wide variation in results may prohibit the development of useful diagnostic thresholds for NIR optical systems [60, 76]. Wide biological variability in vascular measurements is a known barrier to research in this field [96] and this is also reflected in suboptimal reproducibility in alternative modalities for measuring bone tissue haemodynamic markers such as MRI [97, 98].

Variability is likely to be affected by the heterogeneity of bone tissue and the small sampling volume of NIR optical systems (particularly LDF) with sampling of small arterioles or less vascular trabecular striate potentially altering readings. It is important to tease out what variation in results is attributable to measurement error and what reflects normal

physiological ranges. Likewise, most studies typically used only one, or a small group, of operators. Few studies took repeat measurements, or multiple readings at adjacent sites, which is suggested due to this small penetration depth and sampling volume of NIR optical systems.

Other potential factors affecting reliability specific to LDF studies include the comparison of results in studies where the probe is placed non-invasively, directly on the bone surface, or intra-osseously. The sensitivity of probes to movement also means stable probe placements during surgical operations is important and some studies reported holding probes by hand or using bespoke probe holders [40, 51]. Some study designs involved having to move probes in between measurements to facilitate surgery, which can introduce measurement error given the small sampling volume and potential for measuring a different vascular bed when probes are repositioned [77, 81]. In addition, as these LDF studies were intra operative the effects of anaesthesia, blood loss during surgery and direct impact of surgery cannot be discounted as sources of error [41]. When placing probes intra-osseously, the effect of drilling on intra-osseous blood flow is unknown and flushing of the probes is required to remove clotting around the measurement site, which could otherwise prohibit flow and affect readings.

Quality Assessment

An overview of quality assessment ratings is presented in Supplementary Materials 2. A general methodological issue with many studies was the poor description of inclusion and exclusion criteria, recruitment strategies, and summary information of important participant demographics. In the absence of specific details, this opens many studies to potential criticism of selection biases. Similarly, most feasibility studies involved small cohorts of healthy, young and predominately normal BMI participants, raising concerns around the generalisability of non-invasive applications of NIR systems in wider demographics and

disease states. Many studies also included small sample sizes of participants without sample size justification.

Attrition or incomplete results were rarely directly addressed. How incomplete results are handled can lead to biases in the accuracy of results and so it is important these are reported in context with study findings, especially at the early stages of the technological development of NIR optical systems. Generally, most studies had a low risk of performance and reporting bias as testing protocols were clearly pre-stated and all participants received the same testing.

In the case of studies investigating the potential feasibility of NIR optical systems on healthy participants, detection bias was considered generally low, despite studies not always reporting if testing and data analysis was strictly protocoled, or if acquisition and data analysis was blinded to participant information/status. However, in studies investigating different sub populations for physiological differences, this was deemed a more significant potential bias risk, especially when LDF or oxygen saturation with NIRS was used as an outcome measure, where probe placement can be easily adjusted for minor subjective corrections in results, or the most suitable data could be selectively sampled for data analysis. It is acknowledged that with intra operative LDF studies that in most cases LDF operators were not blinded to their participant status as they were likely performing the surgical procedures. As such, detection biases are hard to avoid.

Studies were all also deemed at risk of "other biases" as there are inherent unknowns around the use of NIR optical systems for these applications in bone tissue, as relatively weak validation exists. Along similar lines many studies involving NIRS and PPG systems reported use of bespoke made systems, reducing the applicability of results as there is evidence for systematic differences in haemodynamic measurements across commercial systems from different manufacturers [99].

There was also an applicability issue evident when considering intra-operative LDF findings to guide clinical practice or normal physiology. Often studies found reduced blood flux at various stages during surgical interventions, but without the ability to take pre and post-operative readings the clinical importance of these findings is hard to distinguish. Likewise, obtaining healthy control data is also ethically difficult given the invasive approach taken. Similarly, some studies only presented relative percentage changes in haemodynamic markers with time. Whilst this demonstrates the responsiveness of NIR optical systems in bone, the applicability of these results is limited without development of absolute haemodynamic quantitative markers and threshold results for normal physiology that can guide research into diseased states.

Discussion

A large number of studies have been identified utilising NIRS, PPG and LDF systems to investigate bone tissue either non-invasively or intra-operatively. The wide heterogeneity in anatomical sites and investigated applications demonstrates the demand for the types of information NIR technology promises. The studies identified are predominately early stage proof of concept type work which often illustrate the promise for future clinical and research applications. However, there are a wide range of challenges that require addressing to advance this field of research in bone health.

The need for further work on the reliability and reproducibility of NIR optical systems for repeat measurements across different operators and participants has been identified. Likewise, continued investigation around whether variability is biological or equipment based (or both) is important, as this is still not clear from the literature. If physiological variability is wide at an individual level, NIR optical systems may be unhelpful for development of individual diagnostic thresholds, but NIR research could perhaps still

elucidate important haemodynamics differences between sub populations of interest given the current lack of alternative research tools.

Few studies attempted to validate NIR optical system results against an external comparator or reference standard, such as microangiography, MRI protocols, nuclear medicine and PET protocols. However, those that did presented promising results [50, 56, 82]. External validation remains crucial to give credence to future NIR optical systems. Alternatively, confidence could be gained through correlation of other relevant indicators of bone health, such as bone density, blood markers of bone metabolism, or longitudinal patient follow up when used to guide operative cases.

Establishing the generalisability of results is also crucial to the development of these technologies. This includes gauging the expected normal physiological variability expected between different ethnicities, ages, genders and body habitus as well as during the operative state. It appears the influence of overlying tissue on non-invasive measurements requires careful consideration but may be overcome with continued technological advances. As always, patient tolerability of protocols should also be considered, as well as ruling out any potential negative impact of intra-operative use of LDF, which was not addressed by the studies identified.

Technological advances in NIR optical systems holds the key to the future of this application. The development of time-resolved NIRS systems promises the ability to measure absolute concentrations of oxygenated and deoxygenated haemoglobin non-invasively with the patient at rest. This facilitates easier measurement protocols and more appropriate data comparison between participants. It may also help to address some of the variability in measurements between different tissue types resulting from the significant variability in light scattering. Likewise, the possible development of commercially available broadband NIRS systems can

allow the potential measurement of other relevant components of bone tissue such as mineral, lipid, collagen and water concentration [8, 22, 29, 30]. With improved probe design the ability to measure deeper tissues may also be feasible in the future.

Further work is required before NIR optical systems can be considered a valid and reliable research tool of vascular bone health. However, the wide and varied literature base identified in this review ultimately highlights the strong promise of this application of NIR optical systems, which potentially offers real time, safe and inexpensive measurements of bone tissue haemodynamics.

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