

Application of high-resolution peripheral quantitative computed tomography in a clinical setting

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IMPACT PARAGRAPH

The bones that form our skeleton have a complex structure. They consist of a dense shell of bone on the outside, called cortical bone, and a complex honeycomb-like network of thin bars and plates of bone on the inside, called trabecular bone. To measure the structure of the cortical and trabecular bone ('bone microarchitecture'), detailed scans are needed that can determine this microarchitecture. DXA (dual-energy X-ray absorptiometry) is routinely used in hospitals to assess bone density, but DXA-scans are not detailed enough to measure bone microarchitecture. Also the scans of the currently used CT- and MRI-scanners in hospitals do not have enough detail for the measurement of bone microarchitecture. Bone microarchitecture can be assessed by performing a bone biopsy for inspection with a microscope, but bone biopsies are highly invasive as they require removal of a small piece of bone from the body. High-resolution peripheral quantitative CT (HR-pQCT) is a special CT-scanner that can generate highly detailed scans, which makes it possible to non-invasively measure the microarchitecture of bones in the region of the lower arm and hand and of the lower leg and foot ('peripheral bones'). In combination with mathematical computer models, it is also possible to estimate bone strength from HR-pQCT scans. Besides that, HR-pQCT can be used to evaluate fractures in peripheral bones in high detail.

In this thesis, we studied the use of HR-pQCT to analyze bone microarchitecture and strength in two rare and genetic disorders, the first being OI (osteogenesis imperfecta). Patients with OI or the 'brittle bone disease' have brittle bones due to defects in bone structure and bone material. As a result, they often have many fractures during life. DXA does not fully explain this high fracture risk in OI. From our study, we learned that HR-pQCT can be used to measure bone microarchitecture and bone strength in most patients with OI, which provides insights into the unique structure of the bone in these patients. These insights may help to improve our knowledge on how patients with OI can be treated. This is important because there is no cure for OI, and the optimal treatment for the poor bone structure in OI is not yet known. Our study also showed technical issues when using HR-pQCT in OI patients. First, it is important to take the short limbs and bone deformities (for example bending) of patients with severe OI into account because they may influence the scan location and thereby the HR-pQCT results. Second, we observed large empty spaces in the trabecular bone of patients with OI, which can influence the interpretation of the HR-pQCT results. This knowledge is important when using HR-pQCT in OI in future studies and in clinical practice.

The second rare and genetic disorder that we studied was FOP (fibrodysplasia ossificans progressiva). Patients with FOP or the ‘stone man disease’ become increasingly stiff during their life because their muscles, tendons, and ligaments slowly turn into bone. It means that bone is forming over time in these patients where it normally does not exist (‘heterotopic ossification’ or ‘HO’). As a result, the mobility and independence of patients with FOP worsen over time, and patients do not get old because there is no cure for FOP and no treatment for HO. Little is known about the HO bone in patients with FOP, and bone biopsies cannot be taken to study HO in FOP patients in detail because bone biopsies can lead to new HO. We explored if HR-pQCT can be used to study the HO bone in patients with FOP. We could visualize and measure the microarchitecture of HO bone and learned how HO bone fuses with the neighboring skeletal bone. These insights may help to improve our knowledge on how to treat HO in FOP. However, we experienced large difficulties with taking HR-pQCT scans in the FOP patients due to the patients’ limited mobility. HR-pQCT scans can also only be taken in the region of the lower arm and hand and of the lower leg and foot, but HO often starts in the back and neck in patients with FOP. Therefore, we recommend to use new high-detail clinical CT- or MRI-scanners in FOP because such scanners have a larger gantry than HR-pQCT scanners. A larger gantry makes it easier to use in case of a limited mobility and enables scanning of all bones and not only of peripheral bones. Although these scanners may not reach the same resolution as we obtained using HR-pQCT, it is expected that their scans can reveal details of cortical and trabecular bone.

In this thesis, we also used HR-pQCT to study the effects of treatment with anti-osteoporosis medications on bone microarchitecture and bone strength, specifically in GIOP (glucocorticoid-induced osteoporosis) and PLO (postpartum- and lactation-associated osteoporosis). GIOP and PLO are both forms of secondary osteoporosis, and DXA does not fully explain the increased fracture risk associated with these two diseases. GIOP is a common form of secondary osteoporosis, and it is caused by treatment with GCs (glucocorticoids) such as prednisone. GC-treatment is prescribed in many diseases to lower inflammation such as inflammatory rheumatoid diseases, but it also worsens bone structure and bone strength. In our study, we compared the effects of a relatively new medication for osteoporosis (denosumab) with the effects of an already longer available medication (risedronate). We showed that denosumab can be beneficial in patients who start with GC-treatment and in patients who continue GC-treatment for a longer period because it maintained bone strength in the GC-starters and improved bone strength in the GC-continuers, while risidronate did not. PLO is a rare form of secondary osteoporosis, in which women have an increased fracture risk due to a poor bone structure and bone strength mostly during the third trimester of pregnancy and the first months after giving birth to their child. The

woman in our study had severe back pain starting during pregnancy and multiple fractures in her spine. She was treated with two anti-osteoporosis medications, and we could monitor the effects of this treatment on her bones using HR-pQCT. HR-pQCT can thus give insights into the specific effects of a medication on the cortical bone and the trabecular bone, which may help in deciding on the best anti-osteoporosis treatment option for specific defects in bone microarchitecture.

Finally, we used HR-pQCT in this thesis to evaluate fractures in two peripheral bones, the first being the distal end of the radius. Distal radius fractures, or wrist fractures, are common fractures, among others in postmenopausal women. They can reduce the functioning of the wrist if they are not healing well. The treatment of a distal radius fracture typically consists of immobilization in a cast, but it is unknown what the optimal duration is to wear the cast. In previous studies in our group, it was found that HR-pQCT can be used to study distal radius fractures in postmenopausal women. In these studies, changes in the fracture region were seen early during the healing process due to the formation of new bone. In this thesis, we developed a new method using HR-pQCT to measure this early bone formation and the effects of this bone formation on the strength of distal radius fractures. This method gives more detailed information about the progression of the fracture healing process than can be obtained using currently available imaging techniques. Such information may improve our knowledge about how to optimally treat a distal radius fracture and may eventually help in deciding how long a cast should be worn. Our method may also be beneficial for other clinical applications, for example to get insights into the effects of anti-osteoporosis medications that form new bone.

The second fracture location that we studied was the scaphoid bone, a small bone in the hand close to the wrist. The application of HR-pQCT to the scaphoid bone and especially to scaphoid fractures was novel. Scaphoid fractures are the most common hand bone fractures, and they are very difficult to diagnose with current diagnostic procedures. A scaphoid fracture that is missed or diagnosed and treated with delay has a high risk of not healing. This can lead to a painful wrist movement and an impaired wrist function on the long term. Therefore, patients get a cast when a scaphoid fracture is suspected and come back to the hospital 1-2 weeks later for a second inspection, even when no scaphoid fracture is seen on the first X-ray. This procedure leads to many unnecessary cast immobilizations. In this thesis, we studied the diagnosis and healing monitoring of scaphoid fractures using HR-pQCT. Because this application was new, we first showed that HR-pQCT can be used in patients with a suspected scaphoid fracture and developed an HR-pQCT protocol for this application. Thereafter, we found that HR-pQCT is much better than standard CT for the diagnosis of scaphoid fractures at the second visit in the hospital. We also studied the complex, cashew-

nut-like shape of the scaphoid bone using HR-pQCT and found that the shape could be associated with the presence of a fracture. Together, our studies showed that HR-pQCT is superior in diagnosing scaphoid fractures. We therefore recommend to standardly use HR-pQCT at the second visit, and future studies should investigate if HR-pQCT can also be used at the first visit. If HR-pQCT is not available, we would recommend to study the use of new high-detail CT- or MRI-scanners because the standard imaging techniques can thus miss scaphoid fractures. Besides that, we showed that HR-pQCT can be used to monitor the healing of scaphoid fractures and that this healing process differs from the healing process of distal radius fractures. These insights may improve our understanding on the optimal treatment for scaphoid fractures, which is not yet known for every type of scaphoid fracture. This may further reduce the risk of non-healing of these fractures.

The studies in this thesis showed the value of HR-pQCT in a clinical setting in addition to current imaging techniques such as DXA, plain radiography, and standard CT. Therefore, we are currently integrating the HR-pQCT scanner in the routine clinical workflow in our hospital (VieCuri Medical Center). This integration makes it possible to assess bone microarchitecture and bone strength in detail in patients with metabolic bone disorders and to collaborate with other top clinical hospitals and academic hospitals in the Netherlands. The cost-effectiveness of HR-pQCT is not yet known, but this should be determined considering the rising healthcare costs. If cost-effective, HR-pQCT or in general high-detail CT and MRI should become available in more hospitals. With that, this thesis gives an impression of what could be possible in future clinical practice when current CT- and MRI-scanners have been further developed to assess bone microarchitecture and bone strength.