Imaging of the cardiorenal syndrome and visceral fat

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Chapter 10

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GENERAL DISCUSSION AND SUMMARY

The aims of this thesis were to study the potential utility of imaging biomarkers in the clinical management of cardiorenal syndrome, and to investigate imaging-based quantification of visceral fat, in particular the MRI-based quantification of renal sinus fat volume in patients with type 2 diabetes mellitus. In **Chapter 1** we gave a general introduction of visceral adipose tissue, renal sinus fat and the cardiorenal syndrome. We addressed current difficulties in the clinical management of cardiorenal syndrome. Following the general introduction, the fat accumulation around and within the kidney was reviewed in **Chapter 2**, highlighting the imaging-based quantification of perirenal fat, renal sinus fat and renal parenchyma triglyceride. Following the two chapters, **Part 1 (chapter 3-6)** focused on visceral and renal sinus fat as potential clinical imaging biomarkers, and **Part 2 (chapter 7-9)** investigated the cardiorenal interconnections.

PART 1. CLINICAL STUDIES ON VISCERAL/RENAL FAT

In **Chapter 3** we developed and validated new equations to estimate abdominal VAT volume from simple anthropometric parameters including age, sex, height, weight, waist circumference and hip circumference, based on MRI-derived abdominal VAT volumes of 5772 participants in the UK Biobank. Basic models (age, sex, height, weight) and expanded models (basic model + waist circumference and hip circumference) were constructed by linear regression and artificial neural network (ANN) respectively. The basic and expanded equations demonstrated the adjusted coefficient of determination (R^2) ranging from 0.71 to 0.78, with bias ranging from less than 0.001L to 0.07L in comparison with MRI-measured VAT. Both basic and expanded ANN based equations demonstrated slightly higher adjusted R^2 and lower error measurements than linear regression equations, however without statistical significance. The expanded equations presented higher estimating accuracies (76.9%–90.1%) than the basic equations (74.5%–87.5%) in receiver-operating characteristic curves analysis. An interactive webpage has been built, in which the estimated volume of VAT can be obtained upon inputting the anthropometric parameters (**https://radi-evat.lumc.nl/**).

Chapter 4 investigated the association between abdominal adipose tissue, especially VAT and the occurrence of unsuspected pulmonary embolism (UPE) in hospitalized patients with gastrointestinal cancer. Routine contrast-enhanced chest and abdominal CT scans of 1,974 patients were retrospectively assessed for the presence of UPE, of which 58 patients were identified with UPE and 108 non-UPE patients were matched to form the non-UPE control group. Higher VAT was associated with increased risk of

UPE (odds ratio: 1.96; 95% confidence interval: 1.25, 3.06; p=0.003) adjusting several confounders. Our results suggested that higher VAT rather than subcutaneous adipose tissue was associated with an increased risk of UPE on routine CT scans in hospitalized gastrointestinal cancer patients.

Chapter 5 and **Chapter 6** focused on renal sinus fat volume assessed by MRI. The results of these two chapters were generated from the dataset of the MAGNA VICTORIA studies (ClinicalTrials.gov NCT01761318 (1), NCT02660047 (2)). In **Chapter 5**, the baseline renal sinus fat volume of 95 T2DM patients was compared with that of the 51 healthy volunteers, and the association between renal sinus fat and metabolic traits was investigated. Renal sinus fat volume was larger in T2DM patients compared with healthy controls (15.4 ± 7.5 cm^3 vs. 10.3 ± 7.1 cm^3, p<0.001), and was associated with higher level of glycated hemoglobin (HbA1c). The associations persisted after adjustments for metabolic and anthropometric characteristics. In T2DM patients, higher urinary albumin-to-creatinine ratio was also associated with increased renal sinus fat. **Chapter 6** evaluated the effects of glucose regulation on renal parenchyma and sinus fat volume in West European (WE) and South Asian (SA) patients with T2DM. We found that renal parenchyma enlargement in T2DM patients can be potentially reverted by adequate glucose regulation, while renal sinus fat accumulation responds differently to glucose regulation, showing a reduction in SA patients in contrast to a persistent accumulation in WE patients. The change of sinus fat was not associated with the decrease of VAT or blood lipids, indicating that renal sinus fat might be regulated by different metabolic pathways from those of the general abdominal visceral fat in T2DM patients.

PART 2. CARDIO-RENAL INTERCONNECTION

Chapter 7 reviewed the current difficulties in the clinical management of cardiorenal syndrome, and the emerging role of imaging techniques in the assessment of structure, function and tissue characteristics of the heart and kidneys. Moreover, comprehensive imaging approaches were proposed for future studies for the evaluation of cardiorenal syndrome.

In **Chapter 8**, multiparametric cardiovascular magnetic resonance imaging was applied in end stage renal disease (ESRD) patients. This chapter found differences in structure, strain and myocardial tissue characteristics between the ESRD patients and healthy controls. Increased myocardial T1 and T2 were found in ESRD patients even when no systolic or diastolic dysfunction was detected by routine echocardiography.

Finally, the usefulness of contour-based registration for the post-processing of the T1 mapping images was evaluated in 26 healthy volunteers in **Chapter 9.** Myocardial

extracellular volume fraction (ECV) based on T1 mapping technique is a promising imaging biomarker for the diagnosis and prognosis of various cardiovascular diseases. This chapter found that contour-based registration could optimize the image quality and improve the precision of ECV quantification in cases demonstrating ventricular misregistration among source images.

CONSIDERATIONS

Several considerations of the study methods need to be taken into account when interpreting the results of this thesis. Firstly, the application of the equations developed in **Chapter 3** should be limited to middle-aged and elderly White population, since they were developed using data from participants aged 45-76 years and white participants only. In addition, external validation was not available in this study, thus the estimation capacity of our equations might vary in external samples. **Chapter 4-6, 8 and 9** are limited by the single-center small sample sizes. The study design in these chapters does not allow an interpretation of causality regarding the associations between visceral fat/ renal sinus fat accumulation and clinical characteristics. Potential reverse causation cannot be excluded in the multivariable analysis, and the number of adjustments are constrained by sample size. In addition, the exact risk of unsuspected pulmonary embolism in **Chapter 4** may be underestimated because routine contrast-enhanced CT protocol was not a dedicated pulmonary angiogram. **Chapter 5** and **Chapter 6** are limited by the lack of gold-standard glomerular filtration rate. Increased myocardial T1 and T2 values may also exist in patients with ischemic cardiovascular disease, which might not be completely excluded in **Chapter 8**, as none of the subjects underwent coronary angiography or contrast-enhanced MRI. **Chapter 8** is also limited by the overlap in all the tissue characterization and strain parameters of the patients with those of the controls, which undermines the independent clinical value of each parameter. In **Chapter 9** we only evaluated the effect of contour-based registration on T1 mapping images obtained by MOLLI sequence. Therefore, our findings may not be expanded to other T1 mapping sequences such as shMOLLI, SASHA and SAPPHIRE.

FUTURE PERSPECTIVES

The work presented in this thesis focuses on clinically applicable tools based on imaging techniques in the aspects of cardiorenal syndrome and visceral fat. Further studies are needed to achieve broader implementation of these tools in clinical settings.
First of all, external validation is required to test the estimation capacity of our eVAT

equations in different cohorts. Moreover, the clinical value of our equations need to be investigated in a large population with long term clinical outcomes. CT/MRI-derived VAT is a superior predictor of adverse clinical outcomes in cardio-metabolic diseases over conventional indices such as BMI and waist-to-hip ratio (WHR) (3). It remains to be validated whether the VAT volume estimated by our equations could be used to improve risk stratification and prognosis of cardio-metabolic diseases.

In this thesis, renal sinus fat volume was obtained by semi-automated segmentation based on thresholds of the signal intensities, during which considerable manual correction was still needed. This time-consuming quantification method could limit the scale of clinical application of renal sinus fat. With the rapid development of auto-segmentation techniques based on deep learning algorithm, it would be a promising project to develop a fully automated tool for the 3-dimentional segmentation of renal sinus fat. Although longitudinal change of renal sinus fat volume was observed in T2DM patients with statistical significance in ethnic subgroups, the absolute volume changes were very small. These results need to be validated in larger populations with longer follow-up periods in the future. In addition, the underlying mechanism of the difference in the changes of sinus fat between SA and WE patients could be multifactorial, which requires further studies to identify the key contributors of the changes of renal sinus fat after glucose regulation. Moreover, whether a larger decrease of sinus fat indicates an improved prognosis remains to be elucidated.

Multi-modality and multiparametric imaging techniques have been applied for cardiovascular diseases and kidney diseases and offer opportunities for the evaluation of cardiorenal syndrome. In this thesis, a consecutive and synchronous imaging strategy tracing the natural history of cardiorenal syndrome is proposed. In addition, we propose a multidisciplinary approach involving cardiologists, nephrologists and radiologists to improve the prospect of research studies and clinical management of cardiorenal syndrome in the future. Type 4 cardiorenal syndrome could be a suitable subtype to start with the consecutive and synchronous imaging strategy. This thesis shows a potential value of MRI in detecting subclinical changes in the myocardium in ESRD patients. Further studies are required to evaluate the overall diagnostic and prognostic values of these imaging biomarkers in combination.

SUMMARY

The equation we developed in **Part 1** for the estimation of abdominal VAT volume could be a cost-efficient alternative for studies in which CT/MR examinations are only for the measurement of cross-sectional VAT area. Using the webpage we built, general practitioners and epidemiologists can easily estimate VAT using simple anthropometric

parameters. The association of abdominal VAT with unsuspected pulmonary embolism was further explored in Part 1. Our findings suggested that VAT measurements during tumor staging for high risk populations (i.e. obese patients) could be recommended in clinical scenarios. We also demonstrated the feasibility of volumetric quantification of renal sinus fat based on high-resolution MRI, which yielded high intra- and inter-observer reproducibility, enabling our assessment of the effect of glycemic control on renal sinus fat in T2DM patients. Our findings shed light on the clinical value of renal sinus fat volume in early identification and treatment evaluation of diabetic kidney disease.

In **Part 2** of this thesis we summarized the advantages and disadvantages of different imaging modalities in the evaluation of cardiorenal syndrome. In addition, we proposed that serial ultrasonography or non-contrast MRI scans can be incorporated for simultaneous evaluation of both the heart and kidneys in future studies aiming at finding novel biomarkers for cardiorenal syndrome. This proposal was further endorsed by our findings of the multiparametric cardiovascular MRI in ESRD patients, indicating a potential value of MRI in detecting subclinical changes in myocardial tissue composition in ESRD patients without functional abnormality on routine echocardiography.

OVERALL CONCLUSION

This thesis shows the potential utility of imaging biomarkers of the heart, kidneys, and visceral adiposity in the clinical management of cardiorenal syndrome and type 2 diabetes. We explored the methods to quantify visceral fat, and demonstrated the potential clinical implications of a special compartment of visceral fat, renal sinus fat. We summarized the current role of imaging techniques in the clinical management of cardiorenal syndrome, and evaluated the preclinical MRI-derived imaging biomarkers in a group of patients with type 4 cardiorenal syndrome. Our findings could potentially benefit the clinical care for patients with metabolic disorders and/or cardiorenal syndrome. It can be expected that the role of imaging biomarkers will increase in the evaluation of cardiorenal syndrome, both in research settings and in clinical care. Continuous technical developments in quantitative imaging will increase the potential for applying imaging biomarkers in the management of reno-cardiometabolic diseases, and contribute to achieving the goals of personalized medicine.

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