

Quadriceps muscle ultrasound as a new tool for diagnosing muscle wasting in renal diseases

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| Summary

Protein energy wasting (PEW) is a frequent finding in patients with acute and chronic kidney impairment. It is characterized by the loss of patients' protein stores and energy fuels, characteristic of patients with kidney disease. It can be present in all stages of chronic kidney disease (CKD) and acute kidney injury (AKI), however it becomes clinically evident in the most advanced stages of both conditions. A number of metabolic derangements commonly observed in severe CKD and AKI (e.g. metabolic acidosis, inflammation, oxidative stress, and impaired insulin/insulin-like growth factor axis function), acute and chronic comorbidities and the kidney replacement therapy (KRT) *per se*, may have a negative impact on nutritional status. These pathogenetic factors may lead to muscle wasting through the alteration of the balance between muscle protein anabolism and catabolism.

The diagnosis of evaluation of PEW is usually based on a comprehensive assessment including patient history, physical examination, evaluation of nutrient intakes, biochemical markers and screening methodologies that provide a global picture of patients' protein and energetic reserve, as well as their nutritional risk. An important part of this evaluation is the assessment of body composition, which refers typically to the quantification of adipose tissue and skeletal muscle mass, with the identification of reduced muscle mass being critical.

Nowadays, several methodologies are available for the estimation/measurement of muscle mass. Imaging techniques such as MRI, CT and DEXA, are considered reference methods. While they could provide a precise quantification of muscle tissues, they are not available for routine patient assessment, while have other limitations regarding patients' safety and/or measurement precision in the presence of fluid overload (in the case of DEXA). Bedside tools are usually preferred because they provide immediate information allowing for prompt identification of patients with muscle loss. However, available techniques such as anthropometrics and BIA/BIS have important limitations intrinsic to the methods characteristics that hamper their use in the renal setting.

The aim of this dissertation is to study the applicability, validity and prognostic capacity of quadriceps muscle ultrasound (US) in patients with acute and chronic kidney disease on hemodialysis. The US technique seems to have all the necessary characteristics to be used as a diagnostic tool for the assessment of low muscle mass: low cost, high availability, no specialized staff, it's an imaging technique, high portability to be used at the bedside of patients. There was a need to investigate its sensitivity, reproducibility, repeatability, and to see if measurements were influenced by fluid status. All these characteristics have been considered in the development of this thesis and the choice of US as a new bedside tool to be applied in patients with kidney impairments for the assessment and monitoring of muscle mass.

In **chapter 2**, we studied the reliability of quadriceps muscle US. In this study, quadriceps RF and VI thickness of critically ill patients with AKI stage 3 on KRT were measured by two assessors. Intra and inter-observer reliability was evaluated using intraclass correlation coefficient (ICC). Results showed that the reproducibility of measurements (comparison

between two assessors) was excellent, with an ICC value of 0.92 (across-site range 0.88 – 0.93). The repeatability of the method (comparison of two measurements within the same assessor) was also very high, with an ICC value of 0.99 (across-site range 0.98 – 0.99) for assessor 1 and an ICC value of 1.00 (across-site range 0.97 – 0.99) for assessor 2. No difference was found in measurements obtained before and after dialysis (11.5 (4.2) vs 11.4 (4.1) mm, $P = 0.2498$), independently from acute body weight changes due to fluid removal. Results from this study showed the quadriceps muscle US is reliable, with good repeatability and reproducibility.

In **Chapter 3**, we compared US with CT, a gold standard technique. Quadriceps RF and VI thickness of patients were blindly assessed at the same leg sites by both US and CT scans to estimate average difference in thickness, agreement and precision of the US methodology in comparison to CT. Results showed that the observed differential bias (between +0.04 and +0.26 cm depending on the muscle site) and the proportional bias (between 82% and 98% of the reference values, depending on the muscle site) were not statistically significant. A minimal loss in precision was found with US, but it was not significant.

In **Chapter 4**, quadriceps muscle US was applied in patients with ESKD on HD for the first time in the literature. After stratifying ESKD patients into subgroups based on nutritional variable cut-offs commonly used to define PEW in this clinical setting (BMI ≥ 23 versus < 23 Kg/m²], albumin ≥ 3.8 versus < 3.8 g/dL]) and malnutrition inflammation score (MIS) status (< 6 versus ≥ 6), RF and VI thickness of patients with worse nutritional status defined by BMI and MIS were significantly lower than those of well-nourished ESKD-HD patients (P value range: $< 0.001 - < 0.05$). In addition, we once again tested whether quadriceps muscle US measurements were affected by the HD procedure, with no differences between measurements performed before and after the dialysis session. In addition, we showed moderate correlations between quadriceps muscle US and other parameters of nutritional status such as BMI, MIS, mid-arm muscle area (MAMA) and a low correlation with serum albumin.

In **Chapter 5**, we report the data of a small study, in which we applied quadriceps RF and VI thickness by US in critically ill patients with AKI at baseline (within 72h of hospitalization) and after 5 days to assess whether US was sensitive enough to detect changes in quadriceps muscle thickness during short periods of time. In that study, muscle thickness decreased by $15\% \pm 13\%$ within the first 5 days of ICU stay ($P < 0.001$ for all sites as compared to ICU admission). At baseline muscle thickness of patients was similar to that of healthy controls, however, after 5 days of hospitalization, patients had lower muscle thickness in comparison to controls. In addition, we identified that patients with more severe muscle loss had a higher probability of prolonged hospitalization, a finding that must be confirmed and further developed in future studies with a bigger sample size.

In **Chapter 6**, we normalized US and anthropometric (MAMA and MAMC) measurements of 181 patients on HD by height² (indexed values) and derived different cut-offs of indexed RF and VI thickness by US, as well as indexed MAMA and MAMC based on the distribution (percentiles)

of measurements in our sample of patients with ESKD on HD and studied the mortality risk predictability of 3 different cut-offs (p10, p25 and p50). Unlike indexed MAMC and MAMA, both proximal as well as distal indexed RF and VI thickness were significantly lower in patients who died as compared to patients who were alive at the end of the follow up period. The AUC values for the prediction of mortality were statistically significant at p25 and p50 for US derived measurements, but not for anthropometry. In the adjusted Cox-regression analysis, the indexed MAMC and indexed distal RF and VI thickness were independently related to mortality at p25 and p50, with the strongest association found when studying the indexed distal VI thickness at p50 (HR 2.16, 95%CI 1.27 – 3.69, P = 0.005).

In **Chapter 7**, we applied the cut-offs of indexed distal VI derived from the study described in chapter 6 in combination with HGS to diagnose sarcopenia and compared its prognostic capacity in comparison to sarcopenia as diagnosed by LTI combined with HGS. The applied cut-off for muscle US corresponded to < 3.44 mm/m² for males and <3.52 mm/m² for females, while the cut-off used for LTI was obtained from an age-matched healthy control group with LTI < 10th percentile. The cut-off values for low HGS were <27kg for males and <16kg for females, as recommended by the revised EWGSOP 2. In this study, the correlation between LTI and QVIT was moderate ($r=0.37$; $p<0.001$). When assessing the association with mortality, the non-adjusted analysis showed that low LTI had no association with mortality (HR 1.16 [95% CI 0.60-2.25], while low indexed VI thickness (HR 2.18 [95% CI 1.12-4.27]) and low HGS (HR 9.08 [95% confidence interval (CI) 2.12-38.8]) showed to increase the mortality risk. In the fully adjusted model, only the combination of low HGS and low indexed VIT thickness was significantly associated to higher mortality risk [HR 3.21 [95% CI 1.37-7.53].

The results of this thesis could generate several implications for the clinical practice in the renal setting. First, US for the assessment of quadriceps skeletal muscle could be included as a reference method for the bedside evaluation and diagnosis of low muscle mass. Second, it could lead to increased awareness and more patients being evaluated for muscle loss, since US is currently available in every ICU and dialysis center, results are immediate and there is no need to invest in expensive tools. Finally, nutritional and physical interventions could be easily monitored during HD sessions by assessing patients' quadriceps muscle status with US. The lack of reference values from a normative population, could drive future research in this field.