Intramuscular fat infiltration in CKD: a marker related to muscle quality, muscle strength and sarcopenia

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Changes in body composition related to chronic kidney disease (CKD) have been well documented in many studies. However, over time the focus of research in this area has shifted from evaluating malnutrition to estimating muscle strength and physical performance. Finally, in the most recent years, a new era of studies began to investigate by measuring and rating the clinical significance of intra- and intermuscular fat infiltration as a marker of muscle quality.

Sarcopenia and muscle fat infiltration

Several studies showed that reduced lean body mass is associated with worse quality of life and higher mortality rates. The latest consensus on sarcopenia by the European Working Group on Sarcopenia in Older People specified low muscle strength as a key characteristic of pre-sarcopenia. Low muscle strength, low muscle quantity, and low muscle quality are diagnostic criteria for sarcopenia, and poor physical performance is an indicator of severe sarcopenia. The consensus updated the clinical algorithm for sarcopenia for measurements of variables that identify and characterize sarcopenia. Recent research established ectopic fat accumulation in skeletal muscles as the major risk factor for cardiovascular disease and associated survival. This sparked an interest in the underlying mechanisms of this process aiming to outline clear criteria and tools to establish it.

Intra- and intermuscular fat infiltration, also known as myosteatosis, represents micro and microscopic changes in the muscle architecture and composition related to the accumulation of adipose depots. Ectopic muscle fat infiltration can occur beneath the muscle fascia and between groups of muscle fibers (intermuscular fat), within the muscle fibers (intramuscular fat), and within the cytoplasm (intra-extra myocellular lipids). Inter- and intramuscular fat can be estimated by computed tomography (CT), while intra-extra myocellular lipids can be assessed by magnetic resonance imaging (MRI). Other tools for establishing and estimating inter- and intramuscular fat infiltration include ultrasound and muscle biopsy. Muscle biopsy represents the gold standard for measuring adipose tissue between muscle fibers.

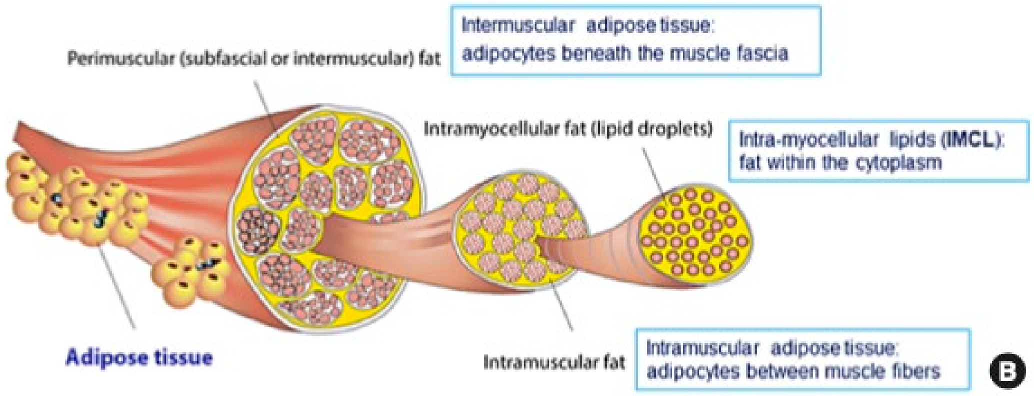

Figure 1. Types of myosteatosis

The most important factors triggering muscle fat infiltration are aging, obesity, physical inactivity, disrupted sex hormones, decreased capillary blood flow, injury, and mitochondrial abnormalities. All these components are associated with chronic inflammation, increased insulin resistance, and reduced muscle strength and activation, eventually leading to lower physical performance and impaired mobility. Muscle fat infiltration causes mechanical changes in muscle fiber orientation, followed by loss of muscle elasticity, muscle tension, and the ability to generate force by contraction.

A longitudinal study of changes in leg composition, muscle quality, and muscle strength, which followed over 1500 elderly patients for five years, showed an age-related increase in intermuscular fat, unrelated to weight gain or weight loss. The weight gain did not prevent the loss of muscle torque in this cohort, despite a discrete increase in muscle cross-sectional area, thus suggesting a diminished muscle quality represented by muscle strength or power or muscle function per unit of muscle mass.

Intra- and intermuscular fat infiltration in CKD patients

CKD patients bear numerous risk factors for muscle fat infiltration: metabolic disorders, including inflammation, insulin resistance, and metabolic acidosis; hyperparathyroidism; increased protein catabolism and protein loss related to dialysis procedure and associated infections; vitamin D deficiency; and sedentary lifestyle. According to the preliminary results by Duque et al., the PTH decline following parathyroidectomy was associated with an increase in muscle strength and an improvement in physical function. Mitochondrial dysfunction in this population is associated with intramuscular fat infiltration and lower physical performance.

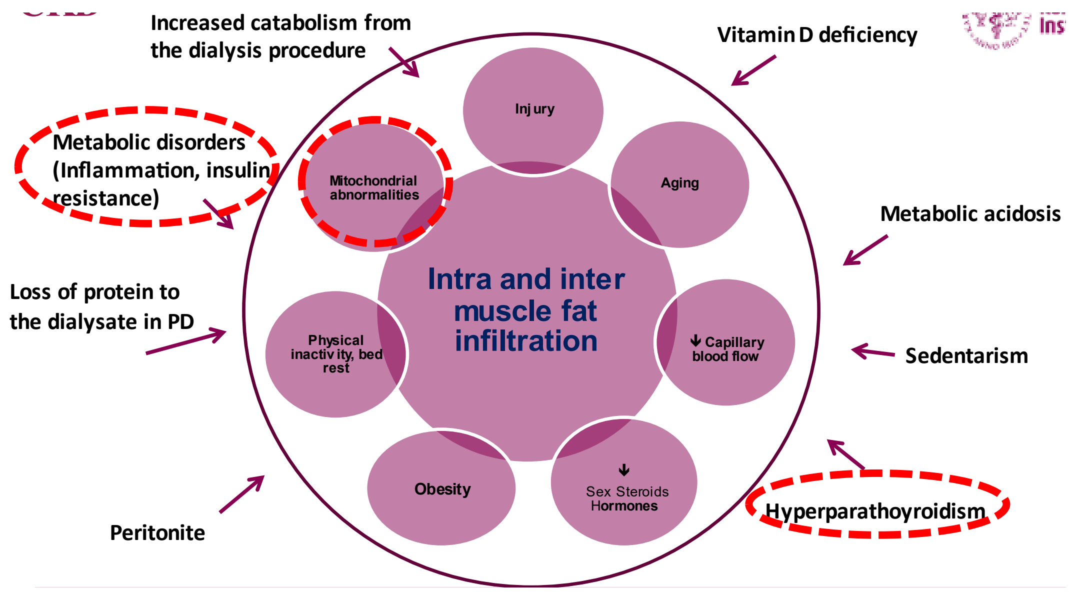

Figure 2. Risk factors for muscle fat infiltration in patients with CKD

Muscle fat infiltration has first been documented in end-stage renal disease (ESRD) patients on peritoneal dialysis by Lindholm et al. nearly four decades ago. However, this finding has not been further elaborated on at that time. A more recent study by Johansen et al. on hemodialyzed patients showed a diminished contractile cross-sectional area of anterior tibial muscle in ESRD patients compared to age and sex-matched controls, even though the total muscle cross-sectional area did not differ significantly between the groups. Furthermore, magnetic resonance images obtained on the day following a dialysis session identified less contractile tissue and more non-contractile tissue (i.e. fat infiltration) in the study group.

Cheema et al. used CT to measure indices of muscle quantity (muscle cross-sectional area) and quality (intramuscular lipid and intermuscular adipose tissue). They showed a significant negative correlation between intramuscular fat and markers of muscle strength and function and a significant positive correlation with age and inflammation markers. Wilkinson et al. assessed the role of muscle quality and size in physical performance in non-dialysis CKD patients by ultrasound images of the rectus femoris. Muscle quality (represented by intramuscular fat) was evaluated using echo intensity, and physical function was measured by the sit-to-stand 60 seconds test, incremental and endurance shuttle walk tests, lower limb and handgrip strength, exercise capacity (VO_2peak), and gait speed. Muscle size remained the largest predictor of physical function, while increased echo intensity negatively correlated with physical performance. Based on these results, the authors concluded that in addition to the loss of muscle size, muscle quality should be considered an important factor that might contribute to deficits in mobility and function in CKD patients. Finally, the preliminary findings by Avesani et al. show an inverse association between intramuscular fat and handgrip strength and the muscle area, and a positive correlation between intramuscular fat and body fat among patients with CKD stages 3 to 5.

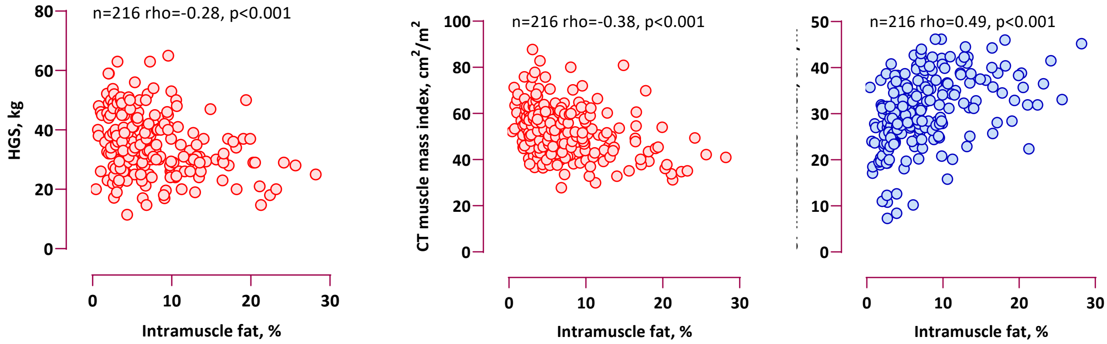

Figure 3. Relationship between intramuscular fat (%) and handgrip strength, muscle mass index, and body fat (Avesani et al. unpublished data)

Fatty infiltration in the muscles is highly prevalent in CKD patients. It is associated with lower muscle quality and muscular strength but is not necessarily linked to reduced muscle mass. Whether this may affect patients' quality of life and survival has yet to be determined. Also, more studies are needed to address possible therapeutic targets for the prevention and treatment of myosteatosis.

Key points

1. Sarcopenia is common among patients with CKD and ESRD, sometimes even in the setting of obesity, and may have important implications for physical performance and survival.
2. Muscle fat infiltration is consistently documented in CKD and ESRD patients by various diagnostic techniques (ultrasound, CT scan, MRI, biopsy).
3. Fatty infiltration in the muscles (myosteatosis) is negatively associated with muscle strength and function in CKD and dialyzed patients regardless the age.
4. Further studies should consider possible therapeutic targets for the prevention and treatment of muscle fat infiltration in this high-risk population.

Further reading

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