Sodium MRI: A New Frontier in Imaging in Nephrology

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Purpose of review

This review focuses on the recent technological advances in quantitative sodium (^{23}Na) MRI to provide a non-invasive measure of tissue viability for use in clinical studies of patients with kidney disease. ^{23}Na MRI is the only non-invasive imaging technique that allows for the absolute spatial quantification of tissue sodium concentration (TSC), providing assessment of the corticomedullary sodium gradient (CMSG) in the kidney, and allowing measures of TSC in the skin and muscle.

Recent findings

^{23}Na MRI of the kidney has demonstrated the sensitivity to measure the CMSG, providing the normal range in healthy subjects and demonstrating a reduction in CMSG in kidney disease and transplanted kidneys. Studies using ^{23}Na and ^{1}H MRI have shown that in humans skeletal muscle and skin can store sodium without water retention, and that sodium concentrations in muscle and skin increase with advancing age. Recent studies have shown that TSC can be mobilised during haemodialysis, and that skin sodium content links closely to left ventricular mass in patients with Chronic Kidney Disease.

Summary

^{23}Na MRI is currently a research technique, but with future advances, ^{23}Na MRI has potential to become a non-invasive renal biomarker to measure tissue sodium storage for clinical studies.

Keywords

Sodium MRI, kidney, skin, muscle, clinical

Introduction

Hydrogen (^{1}H) based magnetic resonance imaging (MRI) and spectroscopy (MRS) is widely used to provide invaluable information on structure and function of the human body, but importantly other naturally abundant nuclei in biological tissue, such as sodium (^{23}Na), can also be imaged. ^{23}Na is the second most abundant NMR sensitive nucleus in the human body. ^{23}Na imaging has the potential to provide complementary quantitative measures compared to ^{1}H MR, however its use has been limited due to the far lower sensitivity of ^{23}Na MRI in the body. Despite the demonstration of sodium MRI in the early 1980s (1, 2), it has only been in recent years that its use has been rediscovered, with the availability of high and ultra-high field (3 and 7 Tesla) MR scanners and advances in MR technology in terms of radiofrequency (RF) coil and pulse sequence design. Applications of ^{23}Na MRI have been shown in the brain, heart, and cartilage, as well as the skin, muscle, and kidney which will be the focus of this review.

Technical Aspects of Sodium MRI

In vivo ^{23}Na MRI is challenging compared to ^{1}H MRI, due to its low sensitivity which is of the order of 3,000-20,000 times less than ^{1}H MRI (organ dependent). This results from the lower gyromagnetic ratio (γ) of ^{23}Na compared to ^{1}H (γ of ^{23}Na is 11.26 MHz/T compared to 42.58 MHz/T), the quantum mechanical property of spin of the ^{23}Na nucleus taking a value of (3/2) compared to (1/2) for ^{1}H, and the low natural abundance of ^{23}Na in the biological tissues. Further, the (3/2) spin results in sodium having a quadrupolar moment, meaning that the MR signal from sodium decays significantly faster than for protons, resulting in a short longitudinal (T_1) and rapid bi-exponential transverse (T_2) signal decay with fast (T_{2f}, 60 % of signal) and slow (T_{2s}, 40% of signal) components.

For implementation of ^{23}Na MRI, the MR scanner needs to be equipped with specialised transmit and receive RF coils tuned to the resonance frequency of sodium nuclei at the respective field strength, but this is now possible on most MR scanners used for research purposes. In addition scanning hardware and pulse sequences need to image faster for ^{23}Na MRI compared to ^{1}H MRI, due to the rapid decay of the ^{23}Na signal. To overcome the low sensitivity of ^{23}Na MRI, signal-to-noise ratio (SNR) is gained by imaging at lower spatial resolution and signal averaging for a number of minutes compared to seconds typically used for ^{1}H MRI. The linear proportionality of the ^{23}Na NMR signal to the spin density then allows for the absolute quantification of the tissue sodium concentration on the basis of a known concentration reference phantom placed within the scanner.

There have been a number of recent comprehensive reviews of sodium imaging (3-6) which describe the challenges of ^{23}Na MR, advances in scanning hardware and imaging techniques, and provide an overview of applications of ^{23}Na MRI. This review focuses on the potential role of ^{23}Na MRI in nephrology, including imaging of the kidneys and the use of sodium MRI to study sodium stored in the muscle and in the skin, suggested to be of relevance in hypertension and chronic kidney disease.

Biological Processes Assessable by Sodium MRI

Sodium is a vital electrolyte in the body and plays several roles including maintaining the volume of blood and fluid and regulating pH within the body. At a cellular level, the concentration of sodium within and outside cells is carefully maintained by the sodium-potassium Na+/K+-ATPase pump, with a large difference in concentration between intracellular (10–15 mM) and extracellular sodium (140–150 mM). This produces a substantial electrochemical gradient, essential for transmitting nerve pulses and pumping ions through cells. This gradient is very sensitive to cell health and changes in this sodium gradient will be reflected in cell integrity. Typically, an increase of TSC indicates a loss of tissue viability and is associated with an increase of intracellular sodium due to the loss of integrity of the cell, and also with an increase of extracellular volume when cells are dying. Thus ^{23}Na MRI could provide direct biochemical markers for cell integrity and tissue viability, or for following changes in tissue viability upon treatment.

One of the main tasks of the human kidneys is to maintain the homeostasis of the body's fluid and electrolyte balance by filtration of the plasma and excretion of the end products. The regulation of extracellular sodium and water balance in the kidney is of particular importance, as this leads to an increasing sodium concentration gradient from the renal cortex to the medulla. A high sodium concentration in the medulla is a crucial for the final concentration of the urine by reabsorption of water. The ability to image the TSC and monitor any changes in the corticomedullary sodium concentration gradient (CMSG) *in vivo* will potentially increase our knowledge of renal physiology and allow the monitoring of changes during a variety of kidney diseases.

Recent evidence showing that sodium is stored in the skin and that interstitial electrolyte balance is achieved by renal and extra-renal mechanisms has identified a need for ^{23}Na MRI to assess skin interstitial sodium *in vivo* under a variety of experimental conditions to evaluate the role of skin sodium in the pathogenesis of hypertension and cardiovascular disease (7). Studies to date indicate these tissue sodium levels are not reliably measured by sampling blood or interstitial fluid. Recent evidence from chemical analysis of tissue electrolyte and water

composition has shown that body sodium content does not always readily equilibrate with water, and cannot be exclusively controlled by the renal mechanisms. (8). In muscle, sodium changes have been linked to several disease states, including diabetes mellitus, hypertension, and cardiovascular risk. It has therefore been suggested that the pathophysiological process of skin and muscle sodium storage is of relevance for health and disease, with sodium accumulation in the extracellular space closely associated with essential hypertension (9).

Sodium MRI of the kidney: normal range in healthy subjects and changes in kidney disease

Sodium MRI of the kidney was first performed in 1988 at 1.5 Tesla (10), yielding low resolution sodium images. It wasn't until 2006, as MR hardware and imaging techniques developed, that sodium imaging of the kidney was performed at 3 Tesla (11), producing the first maps of sodium distribution in the kidney and a qualitative measure of the CMSG.

Normal range in healthy subjects

Quantitative measurement of the sodium concentration in the kidney was first achieved by Haneder *et al.* in 2011 (12), using reference NaCl solutions of known concentration positioned alongside the patient for calibration of the kidney sodium images. Using this method, the effect of water loading on kidney ^{23}Na concentration was measured in healthy volunteers, subjects abstained from water intake for six hours prior to their first ^{23}Na MRI and subsequently ingested 1 litre of water 30 minutes prior to their second ^{23}Na MRI. Water loading caused a reduction in the sodium concentration within the kidney, with a decrease from 63.5±9.3 mmol/L to 48.6±5.3 mmol/L in the cortex and 108.0±10.9 mmol/L to 81.9±10.1 mmol/L in the medulla, but the corticomedullary sodium concentration gradient was not affected. They then advanced these ^{23}Na MRI measures by assessing the corticomedullary gradient (13) using an higher spatial resolution isotropic voxels and investigated the use of the cerebrospinal fluid (CSF) ^{23}Na signal as an internal reference. In 2014, Haneder *et al.* evaluated the feasibility of *in vivo* ^{23}Na MRI of the corticomedullary gradient and measurement of ^{23}Na transverse relaxation times (T_2*) in human kidneys at ultra-high field (7 Tesla) (14), showing mean corticomedullary ^{23}Na signal-to-noise ratio (SNR) increased from the cortex (32.2+/-5.6) towards the medullary pyramids (85.7+/-16.0) and ^{23}Na T_2* relaxation times differed statistically significantly ($P < 0.001$) between the cortex (17.9+/-0.8 ms) and medulla (20.6+/-1.0 ms).

Further studies were performed (15) to ascertain the normal range of corticomedullary sodium concentration in the healthy human kidney, with a mean sodium concentration in the cortex of 58±17 mmol/L (range 27-63

mmol/L) and 99±18 mmol/L (range 126-187 mmol/L) in the medulla. No significant correlation was found between the sodium concentration and age, gender, BMI or glomerular filtration rate (GFR).

Changes in Kidney Disease

Haneder *et al.* performed two studies investigating the feasibility of using ^{23}Na MRI to measure changes in the sodium concentration in the kidney in disease. In the first study, they combined ^{23}Na MRI and functional ^{1}H MRI to measure damage in the kidney exposed to radiotherapy to treat gastric cancer (16), as reviewed by (5) and shown in Figure 1. Functional ^{1}H MRI revealed changes consistent with reduced cell density and tissue oxygenation and ^{23}Na MRI showed a partial loss of sodium corticomedullary concentration gradient in the upper pole of the kidneys exposed to radiation, confirming that loss of CMSG may be an early marker of kidney damage. They further demonstrated the ability of ^{23}Na MRI to detect changes in renal sodium content *in vivo* in a study of patients with central diabetes insipidus (17) by showing that both cortical and medullary sodium concentration decreased by a mean of 17.1±1.1% following intranasal administration of 20μg desmopressin.

In 2014, Moon *et al.* (18) performed ^{23}Na MRI of transplanted kidneys using a dual tuned coil capable of aquiring both proton and sodium images within the same scan session without the need to reposition the patient. This allowed ^{1}H and ^{23}Na images to be overlaid, providing the advantage of accurate segmentation of the medulla and cortex based on the high quality ^{1}H MRI images that could be applied to the corresponding ^{23}Na image. A significant reduction was seen in the sodium concentration in the transplanted kidneys, 153.5±11.9 mM compared to the healthy controls, 192.2 ± 9.2 mM, and a reduction in the CMSG at 8.9 ± 1.5 mM/mm in the transplanted kidney and 10.5 ± 0.9 mM/mm in the healthy kidneys. However, there was no significant difference in sodium levels or CMSG between those transplanted kidneys with acute rejection versus normal function, though the sample size was small with only six patients.

Sodium imaging of the kidneys was also performed by Budjan *et al.* (19) to assess the effect of renal denervation therapy in patients with therapy resistant hypertension. In the two patients studied no changes were found in renal TSC or CMSG at 1, 30 and 90 days following treatment.

Sodium MRI of the skin and muscle: Normal range in healthy subjects; Effects of haemodialysis, and changes in Hypertension, Chronic Kidney Disease, and Acute Kidney Injury

Recent findings using ^{23}Na and ^{1}H MRI have shown that muscle and skin can store sodium without water retention (20), contrary to previous opinion that an increase in sodium intake increases tissue water content. Muscle ^{23}Na MRI is typically performed using a dedicated knee coil to provide sodium images of the calf muscle, whilst assessment of skin sodium requires higher spatial resolution imaging. To achieve this, skin ^{23}Na MRI is typically performed on the calf muscle using customized RF surface coils to provide an in-plane spatial resolution of below 1 mm. Tubes of NaCl (10, 20, 30, and 40 mmol/L) are used as calibration standards to linearly relate the ^{23}Na intensity to ^{23}Na concentration. Typically a ^{1}H image is also collected to measure water content.

Normal range in healthy subjects

In 2013, Kopp et al. (9) demonstrated the important finding that sodium concentrations can be quantified noninvasively in skin and skeletal muscle in humans with ^{23}Na MRI, and that when coupled with conventional ^{1}H MRI imaging, water content can be judged simultaneously. They observed an increase in sodium storage with advancing age, especially remarkable because salt-sensitivity in humans increases with age. Muscle sodium increase was less profound in women compared with men, and muscle sodium deposition was not accompanied by simultaneous water accumulation. In contrast to muscle, increasing sodium content in the skin was paralleled with increasing skin water content. Wang et al. (21) recently investigated gender differences in the patterns of TSC in muscle and skin of the calf muscle using ^{23}Na MRI and showed that sodium content appears to be higher in skin than in muscle for men, however women tend to have higher muscle sodium than skin sodium. Linz et al. investigated the feasibility of high in-plane spatial resolution ^{23}Na MRI in skin at 7 Tesla, demonstrating the benefits of 7 Tesla to assess sodium stores compared to 3 Tesla (22).

Effects of Haemodialysis

Sodium MRI has been used to study the removal of sodium from the skin and muscle during haemodialysis (HD) (23), collecting ^{23}Na images of the calf before and after dialysis treatment. Skin and muscle sodium concentration increased with age in the HD patients, and also control subjects. Younger HD patients (<60 yrs) had similar skin and muscle sodium concentration as healthy controls before HD, after HD the sodium levels in muscle decreased ($P<0.01$) and also tended to decrease in skin ($P=0.1$). Older HD patients (≥60 yrs) initially had a higher TSC than controls, whilst post-dialysis a reduction in TSC was found such that the sodium concentration post-haemodialysis was similar to controls in both skin ($P = 0.37$) and muscle ($P = 0.62$). In addition, this study compared the skin and

muscle ^{23}Na MRI measures to the sodium eliminated by the dialyser, however no correlation was found between sodium removal from plasma and skin or muscle sodium reduction measured by MRI. This study therefore showed that tissue stores of sodium can be mobilised during HD but that secondary clearance of sodium from tissues is less predictable than clearance from the plasma.

Further evidence of potential adverse effects of tissue sodium accumulation was provided by a study by Deger at al. (24), which used ^{23}Na MRI to assess the mechanisms by which insulin resistance occurs in patients on maintenance haemodialysis compared to controls. All subjects underwent hyperinsulinemic-euglycemic-euaminoacidemic clamp studies to measure disposal rates of glucose (GDR) and leucine (LDR) as well as ^{23}Na MRI of the calf to assess the skin and muscle sodium concentration. GDR and LDR levels were lower in HD patients compared to healthy controls, whereas the muscle sodium concentration was higher in HD patients. An inverse linear relationship was found between TSC in the muscle and GDR and LDR in HD patients, a trend not found in the healthy controls. There were no significant differences in skin sodium between dialysis patients and controls. This study hence concluded that excessive muscle sodium may contribute to the development of insulin resistance in patients with end stage renal disease on haemodialysis.

Changes in Hypertension

It has long been recognised that high dietary sodium intake provokes hypertension in salt sensitive individuals but ^{23}Na MRI has made it possible to study the role of tissue sodium storage in this complex pathophysiology. Kopp et al. (9) found that sodium storage in skin of the upper calf increased with age in hypertensive patients as well as controls. Sodium concentration in muscle increased with age in men but not women. When corrected for age it was found that women with refractory hypertension had increased stored sodium in the skin, and men with refractory hypertension had increased sodium in muscle, compared with age-matched normotensive controls. Interestingly spironolactone treatment (in addition to another diuretic) in men with refractory hypertension was associated with lower muscle sodium concentration and a trend towards lower blood pressure (135±16 versus 147±19 mm Hg; P=0.16) than men with refractory hypertension not receiving spironolactone. Further work is required to replicate these complex findings and elucidate the underlying mechanisms.

Changes in Chronic Kidney Disease

Chronic kidney disease (CKD) results in sodium retention and is linked with an increased risk of cardiovascular events, in part due to the high prevalence of left ventricular hypertrophy (LVH) in CKD. The pathogenesis of LVH in CKD is not fully understood and associations with dietary sodium intake have been inconsistent. A recent study found that in patients with CKD, high skin sodium content was associated with greater age, male sex, higher body mass index, higher 24 hour systolic blood pressure and number of antihypertensives, urine albumin excretion, diabetes and cardiovascular disease. Furthermore, skin sodium content in the calf correlated significantly with left ventricular mass (LVM) assessed with ^{1}H cardiac MRI ($r = 0.56$, $P < 0.001$) (25). In multivariable linear regression analysis skin sodium content was a strong determinant of LVM, independent of 24 hour systolic blood pressure and total body hydration.

Changes in Acute Kidney Injury

Acute kidney injury (AKI) is frequently associated with accumulation of extracellular sodium and water but is has not previously been possible to quantitate this accurately. In recent work, Hammon et al. (26) assessed skin and muscle ^{23}Na MRI in in seven patients with AKI, peripheral oedema and weight gain. Before dialysis patients with AKI evidenced higher calf muscle and skin sodium concentration than age matched controls, Figure 2. However, there was no reduction in skin and muscle sodium or water content after four to five cycles of haemodialysis despite this achieving a mean total ultrafiltration volume of 8.36 litres. These observations are in contrast to those in patients receiving chronic hemodialysis and others with heart failure. Limitations of this study include the small number of participants and variation in the haemodialysis delivered. The failure to reduce tissue sodium with acute haemodialysis in the setting of AKI may be due to more severe sodium accumulation in this setting and the unstable condition of patients leading to inconsistent sodium accumulation and mobilisation. The importance of this study is that it demonstrates the feasibility of monitoring tissue sodium with ^{23}Na MRI in the context of AKI. Larger more detailed studies with standardised dialysis interventions are required to explore this topic further.

Conclusion

^{23}Na MRI is a powerful technique providing the potential to image sodium distribution in the kidney, and visualize and monitor changes in the CMSG, a marker of the regulation of extracellular sodium concentration. ^{23}Na MRI can also perform assessment of skin and muscle sodium concentration, and demonstrates changes with age and hypertension. However, currently ^{23}Na MRI is a research technique only, requiring expensive hardware and

software, which are not routinely available on clinical MR systems, preventing routine clinical application. In future, important advances will be made by the fusion of ^{23}Na images with the ^{1}H morphological and functional images, such as perfusion and diffusion, to produce co-located complementary information. With further development ^{23}Na MRI has potential to become a non-invasive renal biomarker of tissue viability and measure of tissue sodium storage for clinical studies.

Key points

- ^{23}Na MRI is the only non-invasive imaging technique that allows the absolute spatial quantification of tissue sodium concentration (TSC).
- ^{23}Na MRI of the kidney has the sensitivity to measure the corticomedullary sodium gradient (CMSG), demonstrating a reduction in the CMSG in kidney disease and transplanted kidneys.
- ^{23}Na MRI has demonstrated an increase in skin and muscle sodium storage with advancing age, and increased tissue sodium content in hypertensive patients.
- ^{23}Na MRI is currently a research technique, but with future advances, ^{23}Na MRI has potential to become a non-invasive renal biomarker and measure of tissue sodium storage for clinical studies.

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Conflicts of interest: none.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

*of special interest

**of outstanding interest

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Patients with AKI evidenced higher calf muscle and skin sodium concentration than age matched controls but there was no reduction in skin and muscle sodium or water content after four to five cycles of haemodialysis despite this achieving a mean total ultrafiltration volume of 8.36 litres.

Figures

Figure 1. A 56-year-old patient after adrenal stereotactic body radiotherapy. As an early effect of radiation therapy, the cortico-medullary sodium gradient and sodium concentration are decreased in the left kidney. Left: color-coded sodium concentration (mmol/L). Right: T_2-weighted morphological sequences. Middle: fusion of ^{23}Na and morphological sequences. Top row: coronal orientation. Bottom row: axial orientation. Previously published. Zollner FG, Konstandin S, Lommen J, Budjan J, Schoenberg SO, Schad LR, et al. Quantitative sodium MRI of kidney. NMR in biomedicine. 2016 Feb;29(2):197-205. PubMed PMID: 25728879. Epub 2015/03/03. eng.

Figure 2. (Upper row) 23Na scans (gradient echo 23Na sequence) of a 61-year-old patient before and after acute hemodialysis therapy. The amount of Na+ in the skin, as well as in the skeletal muscle, did not significantly change. At the far right is a healthy person with little sodium in the skin and muscle. Four tubes containing aqueous solutions with increasing Na+ concentrations (10, 20, 30, and 40 mmol/L NaCl) were positioned inside the coil just below the patient's lower leg. Grayscale measurements of the tubes served as calibration standards for Na+ magnetic resonance imaging (23Na-MRI) of the skeletal muscle and the skin by relating intensity to a content in a linear trend analysis. (Lower row) The same patient before and after acute hemodialysis and the control subject viewed with conventional (1H) MRI (fat-suppressed inversion recovery [IR] sequence). The salt solutions appear white because of their water content. Previously published. Hammon M, Grossmann S, Linz P, Seuss H, Hammon R, Rosenhauer D, et al. 3 Tesla 23Na Magnetic Resonance Imaging During Acute Kidney Injury. Academic radiology. 2017 Sep;24(9):1086-93. PubMed PMID: 28495210. Epub 2017/05/13. eng.

Figure 1

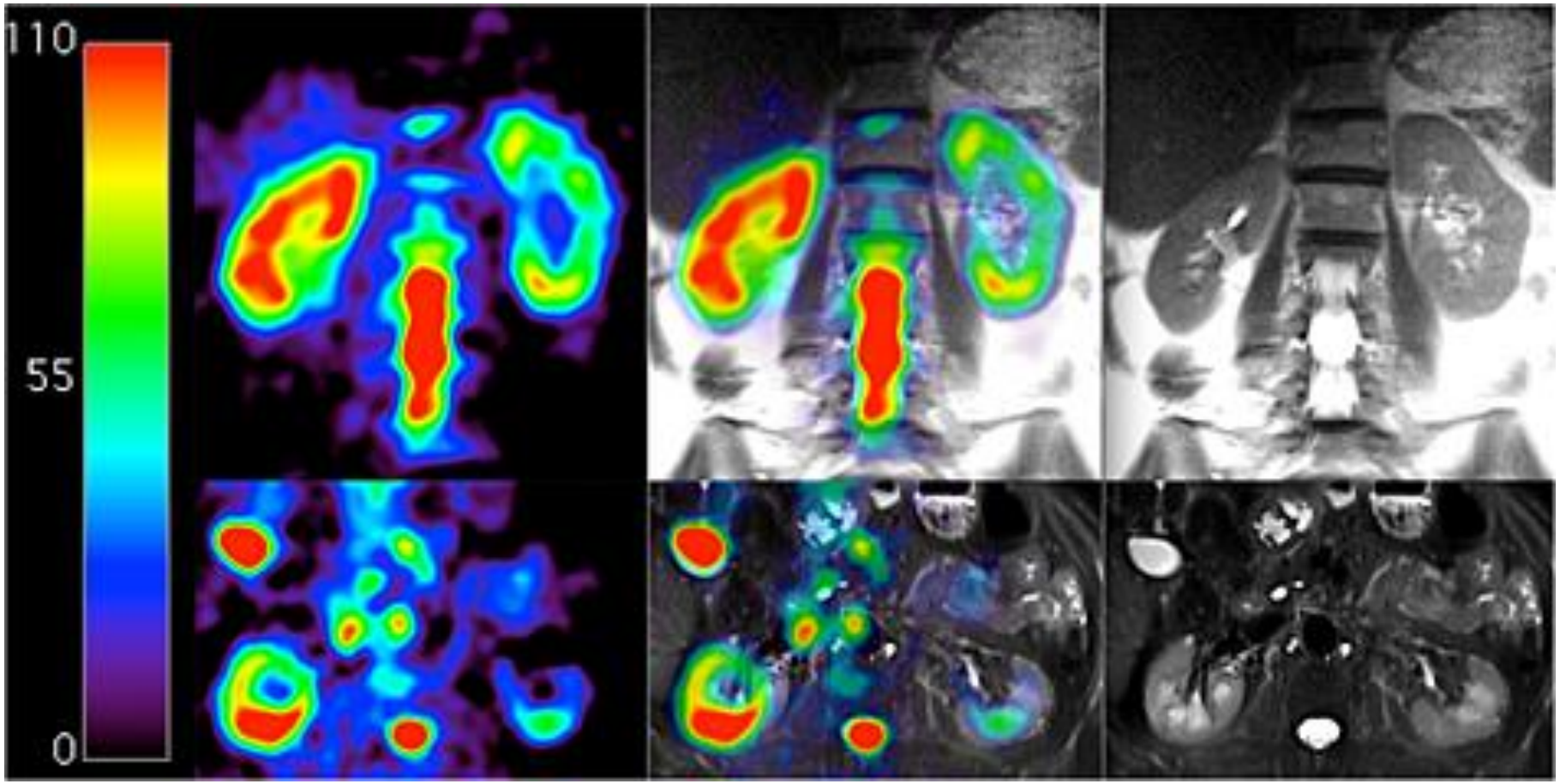
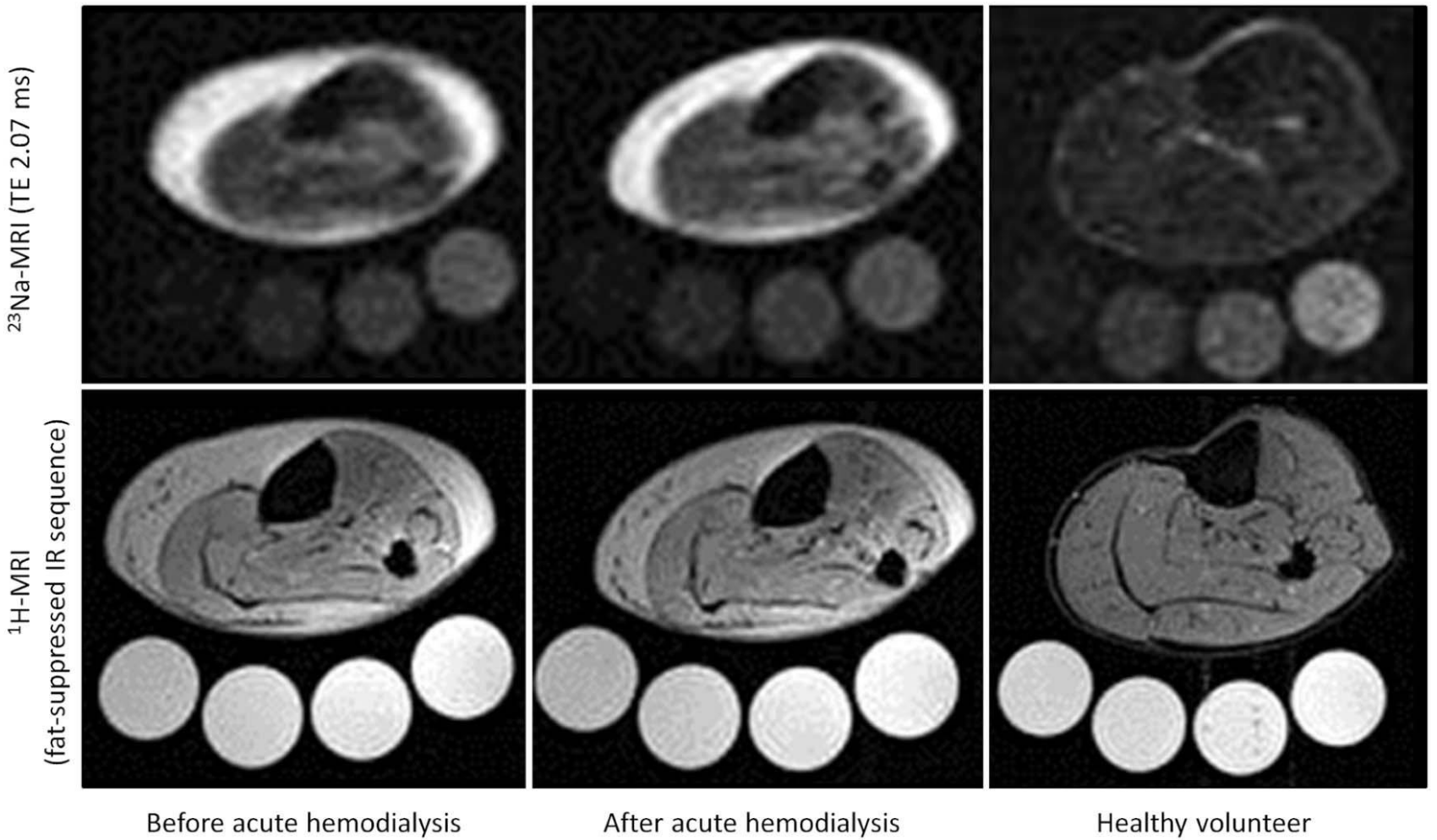


Figure 2


^{23}Na-MRI (TE 2.07 ms)
^{1}H-MRI
(fat-suppressed IR sequence)
Before acute hemodialysis
After acute hemodialysis
Healthy volunteer