6 Gadolinium Retention in Brain and Body: Clinical and Preclinical Evidence

Carlo Cosimo Quattrocchi and Aart J. Van Der Molen

6.1 Introduction to Clinical GBCA Use in MRI and Gadolinium Retention in General

6.1.1 Clinical Use of Contrast-Enhanced MRI

Appropriate use of gadolinium-based contrast agents (GBCAs) in contrast-enhanced MRI is indicated for morphologic imaging, lesion characterization, perfusion imaging, and contrast-enhanced angiography [1]. The added diagnostic value of GBCAs consists of (a) increasing differences of T1, T2, and T2* relaxation time constants between different tissues or normal and pathologic tissues; (b) increasing overall MRI sensitivity; (c) increasing MRI diagnostic specificity by allowing evaluation of different patterns of enhancement and perfusion of differently vascularized tissues; and (d) increasing contrast between intra- and extravascular space in cardiac and vascular imaging.

As a heavy metal in the lanthanide group, elemental free gadolinium is toxic to humans and shows a very long excretion rate with only 1–3% eliminated per day and with the remaining deposited in different tissues including liver, kidney, bone, etc. GBCAs have been developed by chelating gadolinium to organic ligands to decrease toxicity and decrease blood half-life down to about 1 h [2, 3]. Free Gd^{3+}, showing a size similar to that of Ca^{2+}, plays the role of a competitive inhibitor of biological processes requiring Ca^{2+}, can bind to Ca^{2+}-binding enzymes, and affects voltage-gated calcium channels, potentially leading to adverse biological effects [4].

6.1.2 Definitions and Terminologies

On a chemical structure point of view, GBCAs are distinct in two main categories: macrocyclic compounds where gadolinium is caged within the cavity of the ligand and open-chain (commonly called linear) compounds in which gadolinium has a lower thermodynamic and kinetic stability [3, 5]. Gadobutrol, gadoterate meglumine, and gadoteridol are macrocyclic GBCAs, and the remaining are linear forms. Also, within each category, molecules may be differentiated into ionic and nonionic GBCAs, according to the presence of opposite charges or covalent bonds, respectively [6], that have an impact on kinetic stability as nonionic compounds result to be less stable than ionic ones. Although GBCAs are considered as they all behave similarly in each category, differences must be taken into account,

C. C. Quattrocchi (✉)
Diagnostic Imaging, Universita Campus Bio-Medico di Roma, Rome, Italy
e-mail: c.quattrocchi@unicampus.it

A. J. Van Der Molen (✉)
Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands
e-mail: a.j.van_der_molen@lumc.nl

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mainly those related to local extracellular concentration as a main consequence of the compound concentration at the injection site and to relaxivity, i.e., the ability to shorten time constants as a main consequence of the molecular mass [1].

Currently approved GBCAs have similar biodistribution patterns, blood half-lives, and mechanisms of action as well as clearance pathway, mostly secreted through the kidneys. Among these, gadoxetic acid and gadobenate dimeglumine are different as a fraction of the injected dose (50% and 3–5%, respectively) is intracellularly taken up by normally functioning hepatocytes and then excreted through the biliary system [2, 3].

6.1.3 Safety and Efficacy of GBCAs: The Role of Gadolinium Retention

Numerous studies have demonstrated the safety and efficacy of the GBCAs approved for contrast-enhanced MRI with a very low prevalence and incidence of adverse events in phase II–IV clinical trials as well as in post-authorization studies [7–10].

The issue of gadolinium retention in tissues emerged with the first description of the nephrogenic fibrosing dermopathy by Cowper in 2000, leading to what was afterwards called nephrogenic systemic fibrosis (NSF) by Grobner in 2006. Indeed, patients with severe renal impairment were at high risk to develop this systemic disease within a period of up to months after last intravenous injection of GBCAs. Despite this being out of the scope of this chapter, physiopathology of NSF has then been related to the retention of gadolinium in tissues and to its ability to stimulate expression and release of cytokines involved in the development of tissue fibrosis [11–13]. The relationship of the disease with the high rate of tissue retention has then been related to the amounts of gadolinium that persist in the body and that may dissociate from their carrier ligands and/or chelates [14]. As a final end product, through transmetallation, gadolinium may then bind with readily available phosphates, carbonates, or citrates, and form insoluble molecules that deposit into tissues [15, 16]. Preexisting renal failure has been the most prevalent patient characteristic associated with NSF as a clinical risk factor that further decreases the excretion rate of gadolinium forms and prolongs the presence of gadolinium in the body tissues. Nevertheless, an overall epidemiologic evaluation demonstrates that the event of the nephrogenic systemic fibrosis is rare even in the entire population of patients with severe renal impairment and exposure to high-risk GBCAs, especially the linear nonionic gadodiamide which represents the most unstable molecule among all. This suggests that other cofactors have still to be identified to distinguish the subpopulation at maximum risk to develop NSF [17].

However, in the last decade the introduction of specific recommendations such as patient prescreening for renal function, the contraindication of the so-called high-risk GBCAs (Magnevist, Omniscan, and Opti-MARK) in patients with stage IV and V chronic kidney disease, and the restriction of the use of GBCAs to the lowest necessary dose have led to a marked drop of new cases of NSF [18].

In fact, the awareness of NSF and its association with the retention of gadolinium associated with some GBCAs in patients with renal failure has led to introduction of screening for the possible presence of renal disease prior to any GBCA intravenous administration. It is now generally accepted across the world that if renal disease is present, the GBCA agent to be administered is chosen among those recognized at low risk of NSF and the dose is kept as small as possible [19].

However, while alerts on NSF of patients with renal failure have decreased down to zero, the use of GBCAs has been unconditioned in patients with normal renal function in the last 10 years. Indeed, the patient who currently undergoes GBCA administration retains gadolinium into his/her body, although this occurs at a lower rate than in patients with renal failure. Therefore, the event of tissue retention and the deposition of non-chelated gadolinium are currently considered potential risk factors to develop gadolinium-

related toxicity even without impairment of the renal function. Some studies have reported single cases of patients with NSF and gadolinium deposition in multiple organs (including heart, lungs, spleen, kidney, skeletal muscle, and meninges) [20, 21]. To date, the tissues that have been investigated in most of the patients with normal renal function were the bone, skin, brain, and liver, confirming what had been previously observed in preclinical studies.

6.2 Gadolinium Retention in the Brain

6.2.1 Clinical Studies

In 2014 the work of Kanda et al. suggested that the retrospectively observed hyperintensity of the dentate nucleus and the globus pallidus on unenhanced T1-weighted images of a population of patients with brain primary and secondary tumors was related to repeated administrations of GBCAs [22]. Soon after, Errante et al. [23] reported similar findings on unenhanced T1-weighted brain images after multiple injections of gadodiamide in two different unconfounded patient groups, 38 patients with multiple sclerosis and 37 patients with brain metastases. A progressive increase in SI ratios (dentate nucleus/pons signal intensity ratio) was seen in both patient populations. The study demonstrated that the findings were not related to a specific pathology, in addition to confirming the observations of Kanda and colleagues. Several publications were then published in 2015 and 2016. Kanda et al. [24] compared T1 signal intensity after exposure to linear contrast agent (gadopentetate dimeglumine) to that observed after a macrocyclic agent (gadoteridol). Hyperintensity in the dentate nucleus on unenhanced T1-weighted images was associated with prior administration of gadopentetate dimeglumine but not gadoteridol.

Quattrocchi et al. [25] then showed the results from a study including patients that had multiple follow-up brain MRIs for evaluation of meningiomas. In patients with a history of at least six enhanced studies using gadodiamide, a significant increase in the signal intensity of the dentate nucleus on T1-weighted precontrast studies was noted, clarifying that this finding was not related to medical therapy (as could have been the case with the prior studied patient populations). Radbruch et al. [26] also published a comparison of the linear gadopentetate dimeglumine and the macrocyclic gadoterate meglumine, with 50 patients in each group, demonstrating that a change occurred with the first agent, a linear chelate, and not with the second, a macrocyclic chelate. All patients underwent at least six consecutive MR examinations with exclusive use of either the linear or the macrocyclic GBCA. In June 2015, Ramalho et al. [27] published a study evaluating 23 patients who received linear nonionic gadodiamide (5 ± 2.4 injections) and 46 who received the linear ionic gadobenate dimeglumine (4.6 ± 2.1 injections). They found that a significant increase of T1 signal intensity ratio between the dentate nucleus and the middle cerebellar peduncle was seen after gadodiamide but not gadobenate dimeglumine. The rate of change suggested gadolinium deposition in the dentate nucleus also with gadobenate dimeglumine although less than with gadodiamide [27]. In this regard the other commercially available linear liver-specific GBCA, gadoxetic acid, has been associated with T1 signal intensity of the dentate nucleus after a number of doses that are relatively higher than those reported for general-use linear GBCAs such as gadodiamide and gadopentetate dimeglumine [28, 29].

All these investigations suggested a mechanism of progressive accumulation of gadolinium, detectable at conventional MRI and dependent on the structure of the compound chelating gadolinium ions. The high signal intensity on unenhanced T1-weighted images is related to the number of administrations of GBCAs with lower kinetic inertness and this occurs in patients without any kind of renal disease and with a mechanism that is not related to the physiopathology of the disease nor to systemic interval therapy nor to previous brain radiation therapy [25].

These experimental results radically modified two dominant concepts in the medical community: (a) Gadolinium is not completely eliminated from the body about 24–48 h after, i.v., injection in subjects with normal renal function and (b) gadolinium chelates are not unable to cross an intact blood-brain barrier. McDonald et al. [30] in fact published the first report with data on human postmortem specimens in 13 patients with at least four contrast-enhanced brain examinations (using exclusively gadodiamide) and compared them with patients who had not received intravenous contrast agents. Neuronal tissue from the contrast group demonstrated up to 59 μg gadolinium per gram of tissue (ppm), with a significant dose-dependent relationship correlating with precontrast T1-weighted signal intensity changes. Most of the gadolinium deposits were observed in the endothelial layers of brain vessels and a variable part of them (18–42%) were located in the extracellular interstitium, as an effect of crossing an intact blood-brain barrier. No gadolinium was detectable in the neuronal tissue of control patients. McDonald et al. in fact found gadolinium inside the nervous tissue, not only in the globus pallidus and in the dentate nucleus but also in the pons and in the thalamus at a lower concentration. These findings were then confirmed by a new autopsy study conducted by Kanda et al. [31] on five patients who received at least two total doses of less stable GBCAs. In this last report gadolinium was found not only in the brain gray matter nuclei but also in the frontal lobe cortex, in the frontal lobe white matter, and in the cerebellar white matter (Fig. 6.1).

Investigation on brain MRI scans after more than 35 doses of linear GBCAs confirmed that high signal on T1-weighted images may be observed not only in the dentate nucleus and the globus pallidus but also in many other structures such as the substantia nigra, thalamus, red nucleus, colliculi, superior cerebellar peduncle, caudate nucleus, and putamen [32]. As a counterpart, Radbruch et al. [33] did not observe an increase of T1 signal intensity of the dentate nucleus after more than 20 doses of macrocyclic GBCA.

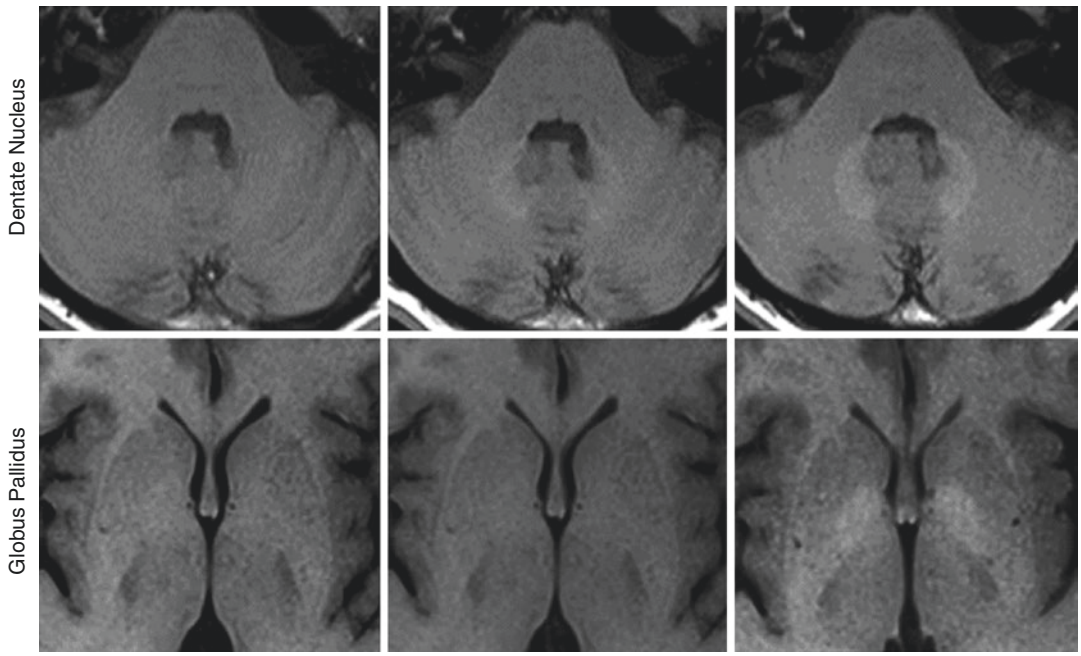

Fig. 6.1 Progressive increase of the same patient's brain at 1st (left-side panels), 6th (middle panels), and 12th (right-side panels) enhanced MRI scan using the linear nonionic gadodiamide

6.2.2 Preclinical Results on Brain Retention (i.e., Animal Studies)

The first preclinical study on gadolinium retention in the brain was published by Robert et al. in 2015 [34]; that work reinforced the idea that T1 high signal intensity and gadolinium retention in the brain are indeed observed only after repeated administrations of a nonionic linear GBCA, but not with similar doses of an ionic macrocyclic agent. They also showed that there is no evidence of a reduction of T1 hyperintensity after a "washout" period of 5 weeks from the last injection, not only in the deep cerebellar nuclei but also in other brain structures [34]. Although the analytical methods used to measure the presence of gadolinium in the brain were not able to distinguish between free and chelated gadolinium, these experimental data highlighted the importance of in vivo dechelation of gadolinium ions from less stable GBCAs and opened questions on the mechanisms of gadolinium ability to progressively concentrate in the brain, regardless of the presence of a renal dysfunction and with a clear dose-effect relationship.

Shortly after, other studies were conducted under preclinical experimental conditions and confirmed that a difference exists in the amount of total gadolinium retained in the brain when comparing different GBCA compounds [35–38]. Recently, evidence from an animal study has shown that gadolinium levels measured in the brain 24 days after the last injection have to be distinguished into three different chemical forms: soluble small molecules, soluble macromolecules, and insoluble forms [38]. The gadolinium contained in the soluble fraction is the component that is slowly secreted and is retained for several weeks; of this, the gadolinium linked to its original molecule or to macromolecules may affect the environment and increase tissue T1 relaxivity, at a sufficient rate to achieve T1 shortening and high signal intensity on T1-weighted images [38]. When comparing different GBCA compounds, Frenzel et al. identified that, although a comparable gadolinium content is present in the soluble fraction of tissue brain homogenates, there is a much higher amount of gadolinium linked to macromolecular complexes for linear than for macrocyclic GBCAs [38].

As it regards the question on the pathway of GBCA entry into the brain, no differences have been found between cerebrospinal fluid penetration and distribution of linear and macrocyclic GBCA compounds [39] and the role of glymphatic circulation has been called out. These data have been supported by the observation of T1 signal intensity increase in the dentate nucleus and globus pallidus after only intrathecal administration of a linear ionic GBCA in a clinical setting [40].

In summary, preclinical evidence is currently available as it regards the mechanisms, amount, and timing of gadolinium retention in the brain. In humans, clinical effects of gadolinium retention in the brain need further research [41].

6.3 Gadolinium Retention in Bone

6.3.1 Clinical Studies

Affinity of most metals and especially lanthanides for the skeleton has been observed via biodistribution studies in the whole body. Nevertheless, to date mechanisms of metal retention and/or deposition in bone are poorly understood mainly because of its structural complexity and dynamic bone tissue remodeling [42].

Non-complexed gadolinium ions and other members of the lanthanide series (e.g., samarium, europium, and cerium) have long been known to deposit in bone tissue of animals and humans.

First observation in humans with a linear GBCA was made by Gibby et al. who studied the retention of gadolinium in human bone tissue collected from patients undergoing hip joint replacement surgery [43]. Further studies compared retention of the nonionic linear gadodiamide and the macrocyclic ProHance [44, 45]. Data confirmed that gadolinium, introduced as its chelated form, is retained for at least 8 years [45]. Also, the demonstration of higher retention in osteoarthritis patients vs. those with osteoporotic

fractures suggests the important role of bone resorption and remodeling on gadolinium retention [45]. However, these clinical studies are partly not confirmed by the fact that ovariectomy-induced osteoporosis has shown no significant difference in total Gd concentration between rats receiving gadodiamide and treated with ovariectomy or not [46].

Recently the bone compartment has shown retention of gadolinium not only after exposure to the linear gadobenate dimeglumine but also after the macrocyclic gadoteridol and gadobutrol with levels measured within a median of 23 times higher than the brain (globus pallidus) in a small group of unconfounded patients exposed to GBCAs [47, 48].

6.3.2 Preclinical Results on Bone Retention (i.e., Animal Studies)

In animal studies, gadolinium retention in the femur has been shown to be 25-fold higher with gadodiamide than with gadoteric acid [46]. At least 21 days after the injection of gadopentetate dimeglumine, more than 96% of the released gadolinium ions were deposited in the bone as a result of translocated Gd ions from dechelation of the Gd-DTPA [49].

When comparing different GBCAs, there appears to be four times more gadolinium in the bones of patients with normal renal function after a nonionic linear chelate than after a nonionic macrocyclic chelate [44]. After 7 days, mice with renal impairment that had received the ionic macrocyclic chelate had three times more radioactivity in their bone than control mice. However, mice with renal impairment that had received an ionic linear chelate or a nonionic chelate had 8 times and 24 times more radioactivity in their bone, respectively [50]. From a literature search on bone retention of gadolinium, the bone residence times of ^{153}Gd have been shown to be more prolonged in the groups of animals that received the linear GBCAs, with half-time values varying from 10 days for gadobenate dimeglumine to 158 days for gadodiamide vs. 4–13 days for macrocyclic compounds [2].

The adult human skeleton is composed of 80% cortical bone and 20% trabecular (cancellous) bone [51]. The annual turnover of cortical bone is in the range of 2–3% vs. 20–30% in cancellous bone [51]. As such, long retention times and highly dynamic remodeling have suggested that human bone may serve as a reservoir for gadolinium into the bloodstream [2].

In summary, current knowledge gaps that need further investigation are the state of gadolinium in the bone, if chelated as initially administered to the patient or in a new compound formed after transmetallation, and the role of different pools of gadolinium complexes (trabecular bone, cortical bone, or bone marrow) in affecting the overall bone metabolism.

6.4 Gadolinium Retention in the Skin

6.4.1 Clinical Studies

Gadolinium deposition in skin biopsies was demonstrated shortly after the described association of NSF with GBCA in 2006. Since then, several clinical and preclinical studies have focused on and detected gadolinium in the skin under the condition of chronic kidney disease or with normal renal function.

In patients with normal renal function, deposition of gadolinium in the skin was not expected or expected to be low [52, 53] until recently Murata showed low deposition of gadolinium in the skin of three patients with normal renal function after exposure to the linear gadobenate and the macrocyclic gadoteridol [47]. More recently Roberts described a single case of high levels of gadolinium deposition in the skin of a patient with normal renal function after 61 contrast-enhanced MRI scans. However, no symptoms or histological alterations were detected. Only increased CD34 immunoreactivity was reported in the connective tissue septa of the subcutaneous adipose tissue, indicating inflammation [54].

The clinical event of "gadolinium-associated plaques" in the skin of patients with and without underlying renal insufficiency suggests that, under conditions that are not still understood, retention of gadolinium may lead to clinical features, even with normal renal function [55].

6.4.2 Preclinical Results on Skin Retention (i.e., Animal Studies)

In preclinical models, Sieber et al. have shown a different potential for different GBCAs to release gadolinium into the skin. They observed fibrosis, increased cellularity, and increased cell swelling in 80% of animals treated with linear gadodiamide [56]. Overall, studies in rodents seem to show that in the condition of normal renal function Gd^{3+} tissue retention is greater after injection of a nonionic linear GBCA (gadodiamide) when compared to an ionic linear GBCA (gadopentetate) and that the lowest level of tissue retention occurs with a nonionic macrocyclic agent (gadoteridol). Also, the high concentration of gadolinium deposited was accompanied by more histological changes (e.g., spindle and stellate cells under epidermis layer and thicker epidermis layer) in the skin of rats treated with gadodiamide compared with gadoteric acid-treated rats [46].

Initial investigations in healthy rats treated with high doses of different GBCAs have shown macroscopic and histological skin changes after gadodiamide but not after macrocyclic agents with a significant higher level of gadolinium retention into the skin after gadodiamide than after macrocyclic agents [56]. An experimental model of repeated administrations of GBCAs, despite a high rate of elimination from the skin of gadolinium within a time period of about 2 months, has shown long-term retention with significantly higher values in animals treated with nonionic linear agents than in those rats receiving ionic linear GBCAs. After treatment with macrocyclic compounds, gadolinium levels in the skin were in the same range of controls [57].

Wang et al. showed that Gd^{3+} concentration was 180-fold higher in the skin of rats receiving the linear gadodiamide than rats treated with gadoteric acid. Ultrastructural changes in the skin after gadodiamide exposure included focal Gd^{3+} deposition/incrustation of collagen fibers with a "halo" formation around some fibers [46].

In summary, gadolinium retention/deposition in the skin is higher with linear than with macrocyclic GBCAs; however, there is still need to further understand the relationship between gadolinium exposure and clinical occurrence of skin plaques, if this is dependent on the cumulative doses of gadolinium and, eventually, the underlying physiopathological mechanisms.

6.5 Gadolinium Retention in Splanchnic Organs

6.5.1 Clinical Studies

Quantitation of gadolinium into the liver tissues has been reported in a group of pediatric hematopoietic stem cell transplant recipients [58]. In these patients, with normal liver and renal function and under the condition of iron overload, they found high levels of total retained gadolinium compared to age-matched controls and a positive correlation between liver gadolinium and iron concentration after exposure to the macrocyclic gadoterate meglumine. Moreover, gadolinium liver concentration was reduced after treatment with chelation therapy with deferoxamine [58].

6.5.2 Preclinical Results from Splanchnic Organs (i.e., Animal Studies)

The retention of gadolinium in splanchnic organs is known from preclinical evidence. Tweedle et al. found that gadolinium retention in liver 2 weeks after injection of GBCAs was three

times greater following the linear and nonionic GBCA gadodiamide compared to the linear and ionic gadopentetate. In both mice and rats, total gadolinium retention in tissues was minimal with the macrocyclic chelates gadoteric acid and gadoteridol [59].

These results were confirmed by Wang et al. who demonstrated the deposition of gadolinium in the liver of rats exposed to gadodiamide or gadoteric acid [46].

Histopathological and molecular changes (apoptosis) in the liver, lungs, and kidney tissues have been observed in GBCA-treated mice [60]. In Balb/c mice exposed to IV injection of different contrast agents, including gadopentetate dimeglumine, a number of changes including reduction in total white blood cell count, increases in serum levels of inflammatory cytokines (IL-6 and TNF-R), and hepatic histopathologic changes (vacuolar degeneration, disorganized hepatic cords) were observed. One concern regards the possibility that gadolinium might be trapped by the reticuloendothelial system (RES) in splenic macrophages, liver Kupffer cells, and hepatocytes, as reported after administration of a soluble gadolinium salt to rats [61].

Under the condition of impaired renal function, exposure to gadopentetic acid increased short-term (3 days after last injection) Gd retention in the liver, spleen, and kidney but did not affect long-term (45 days after last injection) Gd retention. Gadopentetate showed higher Gd retention than gadoterate meglumine. Although Gd retention of the liver and the spleen in the group exposed to the macrocyclic gadoterate meglumine was generally low, impaired renal function increased only long-term hepatic Gd retention [62].

In summary, although gadolinium retention/deposition is now well established to occur in different organs despite normal renal function, the burden of gadolinium retention in splanchnic organs is not well understood as well as the species of gadolinium present and the link to health consequences.

6.6 Clinical Consequences of Gadolinium Retention

Retention of gadolinium in different tissues of patients with normal renal function is currently under study to exclude any potential deleterious effect of gadolinium species on the cellular functions at low concentrations observed in vivo in clinical and preclinical conditions. The brain is the only organ where MR imaging is able to detect a sign of gadolinium retention, the high signal intensity on unenhanced T1 weighted images of the deep brain structures after exposure to cumulative doses of GBCAs. Only analytical chemistry techniques can be used to detect gadolinium in all other organs. While no associated clinical health consequences have been described until now, health consequences cannot be ruled out, and further preclinical and clinical studies are needed.

There are currently only case reports of patients self-reporting nonspecific complaints such as headache, central torso pain, peripheral leg and arm pain, peripheral leg and arm thickening and discoloration, as well bone pain [63, 64].

The current state of the knowledge (see drawing below) is that stability of the gadolinium-based contrast agents affects the gadolinium chelation state with linear GBCAs that tend to dechelate at higher rates than macrocyclic GBCAs. Both, in patients with either impaired or normal renal function, where differences in excretion times may affect the level of tissue retention are conditioned by the specific environment of different organs. No matter whether the intact compound is retained or transmetallation favors the dechelation of gadolinium, in vivo magnetic resonance imaging is able to detect tissue retention only in the brain depending on the interstitial concentration of paramagnetic forms of gadolinium, their relaxivity, and the technical parameters of the MRI clinical setup. The amount of gadolinium that is retained rarely associates with clinical symptoms as most of the exposed patients remain asymptomatic even after multiple administrations of the most unstable of the

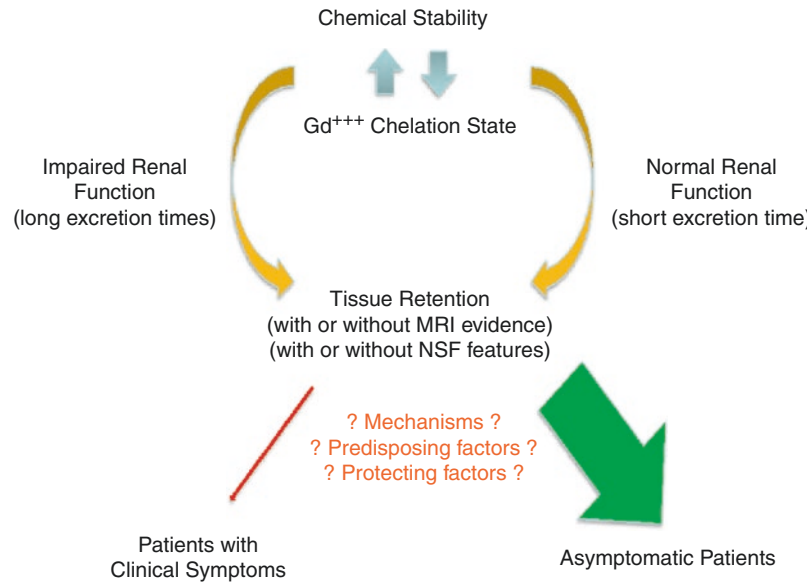

Fig. 6.2 Diagram of the potential link between GBCAs kinetic inertness, renal function and clinical consequences. It should be acknowledged that symptoms have been rarely associated with exposure to gadolinium-based contrast agents while there is no proof that cumulative doses and higher amounts of retained gadolinium are related to a higher risk of clinical consequences

gadolinium-based contrast agents, supporting the idea that genetic vulnerability or other unknown predisposing/protecting factors are involved and need further investigation (Fig. 6.2).

6.7 Concluding Remarks

The use of GBCAs has revolutionized the field of magnetic resonance in the last 25 years. Clinical applications in steady-state parenchymal imaging, MR angiography, and perfusion are now part of routine radiological practice.

There is now evidence that gadolinium can accumulate in tissues regardless of renal function and that linear GBCAs are associated with higher tissue accumulation that is related to their differences in kinetic inertness.

Radiologists as well as nephrologists should be aware of the characteristics of the various agents including chelate stability, relaxivity, and concentration along with the differences in long-term retention in the body and the brain. Further knowledge on this safety issue will be available in the next future and optimization of contrast agent selection and amount to be administered will be a topic of discussion.

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