Gadolinium toxicity: Iron and ferroportin as central targets

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1. Introduction

Gadolinium-based contrast agents (GBCM) are widely used in magnetic resonance imaging (MRI). GBCM were widely considered safe until the discovery of its link with the devastating systemic fibrosing illness, nephrogenic systemic fibrosis (NSF) in 2006, in patients with reduced kidney function [1,2]. Most cases were attributed to less stable linear GBCM such as gadodiamide (Omnisan™) [3,4]. This lead to a “black box” warning by the US Food and Drug Administration (FDA) and European regulatory authorities against using linear GBCM in patients with advanced chronic kidney disease (CKD) and end stage kidney disease (ESKD). Since these warnings were issued, the number of incident NSF cases have dramatically reduced confirming the link between GBCM and NSF [5]. More recently, gadolinium deposition, particularly in the brain, has been described in patients with normal renal function [6–8]. The mechanisms of gadolinium deposition in selective areas of the brain and its clinical consequences are unknown. In this review, we will focus on the pathogenesis of gadolinium toxicity with a special emphasis on its potential direct link to iron homeostasis.

The pathogenic mechanisms of gadolinium toxicity continue to be investigated although several clues have emerged. We will review: 1) the potential role of iron in transmetallation and gadolinium toxicity; 2) link between altered iron homeostasis, iron exporter-ferroportin and cellular mechanisms of fibrosis; 3) a potential link between metal homeostasis and the recently described selective gadolinium deposition in the brain of patients with intact renal function.

1.1. Transmetallation in gadolinium toxicity: role of iron

Linear GBCM such as Omniscan™ and Magnevist™ are the primary gadolinium-based contrast agents that have been implicated in the pathogenesis of gadolinium toxicity and NSF. With their linear gadolinium to chelate structure, thermodynamic stability is lower than cyclic GBCM such as ProHance™[9]. One of the leading theories for gadolinium toxicity is the role of transmetallation where endogenous metals such as iron and zinc attract the ligand to release free gadolinium that deposits in the tissue as gadolinium phosphate [10–12]. Lower thermodynamic stability of the GBCM will facilitate easier transmetallation with endogenous metals such as iron or zinc [13,14].

In support of transmetallation, animal and human studies have demonstrated increased zincuria after linear GBCM administration, particularly at toxic doses. Further, animal models of NSF also demonstrate increased urinary zinc excretion [10,15]. Zinc-dependent transmetallation could not fully explain NSF pathogenesis as exogenous zinc supplementation did not exaggerate the severity of fibrosis in animal models of NSF [16].

Our studies and others have demonstrated iron mobilization in a subset of patients exposed to linear GBCM [13]. In our prospective observation of 2 CKD patients, we observed that GBCM triggered iron mobilization, transferrin oversaturation and induced substantial elevations in serum ferritin. One of these patients required hemodialysis but the patient eventually developed NSF. In a retrospective analysis, we could also confirm that transferrin saturation and serum ferritin levels were higher in ESKD patients with established NSF than in control ESKD patients [13]. In an autopsy study of NSF patients, we further demonstrated that NSF is associated with tissue accumulation of not only gadolinium but also of significant...
1.2. Iron recycling macrophages as a target of gadolinium toxicity (Fig. 1)

While the above discussed studies demonstrate that GBCM induces iron mobilization, our subsequent studies seeking to examine the cellular source of iron identified an important role of CD163+ iron recycling macrophages in gadolinium toxicity [23].

Body iron homeostasis and stores depend on dietary iron absorption and more importantly on erythrocyte and heme turnover mediated by the CD163+ iron recycling macrophages. CD163 pathway serves to endocytose hemoglobin bound to haptoglobin by hepcidin, an endogenous peptide produced by the liver [27]. While studies have suggested a prolonged tissue presence of chelated gadolinium, most studies have shown gadolinium to be deposited in tissues as an insoluble gadolinium phosphate. Collectively, these observations suggest that endogenous free iron-dependent GBCM transmetallation could potentially play a role in the pathogenesis of NSF.

1.3. Cellular iron import in gadolinium toxicity

Transitional polyvalent cationic metals and gadolinium have been shown to perturb cellular iron metabolism and induce increased cellular iron acquisition by myeloid phagocytic cells through transferrin receptor [33]. This would result in increased macrophage iron content. Ghio et al. have recently confirmed these observations. In their study, addition of linear GBCM disrupted cellular iron homeostasis and dramatically increased transferrin-dependent cellular iron uptake and induced an increase in H-ferritin content [34]. These observations along with the findings of our studies indicate that both heme- and non-heme iron import, storage and export pathways are activated by GBCM.

![Gadolinium-based contrast agents](image-url)

**Fig. 1.** Gadolinium-based contrast agents target CD163/ferroportin-expressing iron-recycling macrophages, perturbs macrophage iron homeostasis, and triggers labile iron release. Iron-induced transmetallation of GBCM leads to gadolinium and labile iron toxicity and a pro-fibrotic milieu.
1.4. Labile iron, macrophages and tissue injury in gadolinium toxicity

In our earlier studies, we have implicated a potential role of labile iron or NTBI in GBCM transmetallation [13,14]. Labile iron is defined as free, non-transferrin bound ferrous iron species that is capable of participating in Fenton reaction to induce oxidative stress, lipid peroxidation and tissue injury [35,36]. Labile iron levels are increased in ESKD [37], in patients with tissue iron overload, in those with low transferrin levels, in tissue injury and in patients with hepcidin deficiency. In our studies, we have demonstrated that GBCM not only induces differentiation of CD163+ macrophages but also triggers labile iron release by these cells [38]. Thus, it is likely that a combination of ESKD status, malnutrition with hypotransferrinemia and CD163+ macrophage induction and infiltration in NSF is accompanied by labile iron-mediated tissue injury. Of note, labile iron is known to be pro-fibrotic and has been implicated in the pathogenesis of variety of systemic fibrotic conditions [39,40]. Our recent studies confirm a pathogenic role of labile iron in NSF. We first demonstrated that iron chelator, deferiprone, significantly inhibited GBCM-induced in vitro differentiation of human PBMC into CD163+ macrophages, and reduced their labile iron release. Further, deferiprone substantially reduced CD163+ ferroportin+ macrophage infiltration and dermal fibrosis in a murine model of GBCM-induced fibrosis [38].

Collectively, these observations demonstrate that GBCM targets iron recycling CD163+ macrophages, induces cellular iron import and export, and labile iron release, which participates in systemic fibrosis.

1.5. Brain gadolinium accumulation: potential link to iron homeostasis (Fig. 2)

Several recent studies have revealed that even in patients with apparently normal renal function, repeated administration of linear GBCM are associated with significant quantities of residual gadolinium in brain tissues [6,8,41]. Several recent radiologic and autopsy studies have demonstrated that multiple GBCA doses induce increased T1 signal intensity in the globus pallidus, thalamus, caudate nucleus, and dentate nucleus of brain. Some of these studies have confirmed tissue gadolinium deposition in these brain areas [7]. It is of interest that these brain gray matter structures are intrinsically iron-rich and are specifically affected by neurodegenerative disorders with brain iron toxicity. CD163+ pro-inflammatory macrophages are involved in active regulation of iron and manganese metabolism to protect neuronal tissue that are novel targets to prevent and treat gadolinium toxicity and NSF. Iron-recycling ferroportin-rich cells in structures such as globus pallidus, cerebellar dentate nucleus, thalamus, retina and dorsal root ganglia may similarly be the targets of GBCA in the brain. Further studies are required to understand the role of neuronal iron transport and ferroportin in gadolinium toxicity.

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References


