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The gadolinium hypothesis for fibromyalgia and unexplained widespread chronic pain

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ABSTRACT

Fibromyalgia (FM) is a chronic, painful, heterogeneous, and common disorder carrying a substantial socio-economical burden. It lacks effective cures and its aetiology is still unknown. There exists evidence for central and peripheral neurological contribution to the symptoms but grasping the real source of abnormal nervous system sensitization remains an ongoing challenge. There exists an association between an injury/trauma and the onset of the symptoms, but a causal relationship has not been yet sufficiently supported by scientific evidence.

I postulate a role for gadolinium-based contrast agents and retention of gadolinium in the body. This conjecture breaks the hypothesis of a direct role for a physical injury/trauma per se in favour of an indirect one by the subsequent diagnostic procedures. It creates a new link between retention of gadolinium in the body and painful conditions as FM and unexplained chronic widespread pain reported after a trauma, surgery, or medical illness.

Experimental evidence demonstrates possible retention of gadolinium species in human body, still lacking conclusive answers on their pathological consequences. Notwithstanding, there exist some initial data that report unexplained chronic widespread pain and symptoms of FM in those patients: they are suggestive for pathological consequences associated with gadolinium retention. Besides clear compelling symptoms overlapping, biochemical findings are provided to sustain the hypothesis of a role for gadolinium in the disease process focusing on neurotransmitters, endogenous metal cations, cytokines, and muscle tissue. Experimental findings strongly support the hypothesis of impairment at the cellular, intracellular, and systemic levels in FM. And these data are highly compatible with collateral effects associated with the interference of the gadolinium ion and its pharmaceutical chelates into biochemical pathways in vivo.

The hypothesis presented in this article, along with the support of scientific evidence, links FM and unexplained chronic widespread pain reported after a trauma, surgery, or medical illness to retention of gadolinium in the body. If the hypothesis is confirmed, it could improve diagnosis and prevention, while providing a ground for development of new treatments.

Introduction

Fibromyalgia FM is a chronic, complex, heterogeneous, common, and often disabling disorder [1–4]. In the adult worldwide population, FM prevalence variably ranges from 0.5% up to over 5% [5,6]. However, it can affect also children and adolescents [7]. FM profoundly impacts on working, social, and private life. It can be excruciating and disabling concerning not only physical but also mental, cognitive, and psychological spheres. The symptomatology can be roughly clustered into musculoskeletal symptoms and pain, sleep disturbances, fatigue, neurocognitive and neurological manifestations (including visual and auditory disturbances), mood disturbances, autonomic and neuroendocrine manifestations, and symptoms better known as specific central syndromes, that often belong to patient's past clinical history [1]. Chronic musculoskeletal widespread pain, fatigue, non-restorative sleep, mood disturbances, and cognitive impairment are the cardinal symptoms [1–3]

The aetiology and pathophysiology of FM are both still poorly understood [5,6]. FM lacks an effective cure in the clinical practice and remains a socio-economical burden worldwide [7–9].

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Evidence for central and peripheral neurological

Contribution to the symptoms

The involvement of both central and peripheral nervous system in FM is today accepted, with evidence of dysregulation of pain processing [6]. However, grasping the source of abnormal nervous system sensitization remains an ongoing challenge, together with a proper and timely diagnosis [6].

Evidence for an injury/trauma as a trigger in the onset of the symptoms

There exists clinical evidence [10–14] suggesting an association between a physical trauma (neck injury, first and foremost [12]) and FM (termed 'reactive fibromyalgia' or 'post-traumatic fibromyalgia' [11,10,15], or unexplained chronic widespread pain reported having an earlier trauma, surgery, or medical illness [16]. Nevertheless, the direct causal relationship still remains to be demonstrated in full.

Hypothesis

I postulate a role for gadolinium-based contrast agents (GBCAs) and retention of gadolinium in the body, mainly following diagnostic procedures.

Under this hypothesis the amplified and characteristic pain, the altered sensory processing, the abnormal nervous system sensitization, altered homeostasis, and metabolic abnormalities would be the collateral effects of gadolinium retention in the tissues mainly coming from GBCAs intravenously administered to the patients for contrast enhancement in magnetic resonance procedures but also coming from possible environmental contaminations of anthropogenic origin (see Section 8). In this context, the symptoms would be variably caused by:

- Toxicity of gadolinium exposure for the body in the event of contrast agent dissociation, tissue retention, and particularly long-term persistence in compartments crucially involved in homoeostasis, such as bone tissue;
- Dissociated ligands - mainly sequestrating endogenous divalent cations and reducing their availability for physiological functions – leading to both short- and long-term consequences too;
- Whole complexes stored in the body and thus prone to delayed dissociation.

Background knowledge

GBCAs in clinical practice

Gd(III)-based contrast agents (GBCAs) are soluble metal-ligand complexes of the gadolinium trivalent cation (Gd(III), Gd^{3+}) [17]. They are designed to eliminate Gd(III) toxicity by chelation of the hydrated ion [$Gd(H_2O)_8^{3+}$] with a proper organic ligand (i.e., a poly-amino-carboxylate ligand molecule that cages the toxic ion and coordinates Gd (III) centers by both oxygen and nitrogen atoms) [18,19]. Since their first introduction in the clinical practice in 1988 [20,21], GBCAs have assumed a growing role in clinical radiology both for diagnosis, staging evaluation, and follow-up of several diseases [22]. GBCAs are powerful diagnostic tools with peculiar physical requirements [19,23] and stringent biological demands for non-toxicity as pharmaceuticals and medical diagnostic tools [19]. Several GBCAs have been approved for clinical use until the recent drug warning updates in 2015 (Safety Announcement (7–27–2015),[24]), 2017 Medical Imaging Drugs Advisory Committee Meeting -Briefing Document (7–27–2017) [21], 2018 (New Class Warning (05–16–2018) [25]) by the U.S. Food and Drug Administration (FDA), and until the restrictive revision by European Medicines Agency (EMA) [26].

In vivo toxicity: A role for in vivo dissociation and transmetallation

The safety of a contrast agent is mainly determined by its properties of stability and selectivity in vivo [27,28,18,17]. Because of high toxicity of Gd(III) in biological systems, the dissociation of Gd(III) complexes should not occur to any significant degree [19]. Furthermore, ligands do carry their own toxicity in the event of dechelation (i.e., dissociation of the metal ion from the organic ligand) through transmetallation (i.e., exchanging ions among different ligands in solution) [19]. It is the combination of ion and ligand that highly reduces the toxicity of the two separate components [19]. Kinetic inertness, rather than only thermodynamic stability, is a key feature for in vivo safety [29,27]. In case of poor stability of the complex, selectivity properties of the ligand for Gd(III) over other physiologically available metal cations become crucial for in vivo toxicity. The molecular structure of the ligand and metal affinity to the ligand play a significant role. If the pharmaceutical chelating molecule has a higher affinity for other readily available cations in the surrounding chemical environments than for Gd^{3+}, the lanthanide ion can be rapidly re-bound by a different ligand as soon as it dissociates from the complex [28]. A potential consequence of such inauspicious event includes the long-term retention of Gd^{3+} in the body [28,27]. At the same time, dissociated exogenous free ligands manifest their pathological potential too, provoking deficiency of endogenous cations [27]. This might occur in the event of dissociation but it could also be exacerbated by an excess of ligands in the pharmaceutical formulation [27].

The lanthanide ion Gd(III)

Gd(III) sits precisely in the middle of the lanthanide series, and it shows a varied "cart" of toxic effects at intracellular, cellular, and systemic level often shared with other lanthanides [30–40]. Marked physico-chemical similarities make all them able to significantly and uniquely affect biochemical pathways in biological systems [30,31]. Atomic radii of lanthanide ions (LIs) in aqueous solution [41] are very close to that of Ca^{2+} but other than size, similarities of great biochemical relevance between Ca^{2+} and LIs involve also coordination chemistry, binding behaviour, and donor atom preference, like Ca^{2+} LIs prefer to bind to oxygen donors [31]. Moreover, LIs exhibit interesting flexibility of their coordination geometries that gives them the potential to adjust according to the binding site, and they also can replace Ca^{2+} in a specific, isomorphous manner [31]. The fate of LIs in aqueous solution strongly depends on their surrounding physico-chemical conditions: in vivo, they involve not just parameter such as concentration, pH, and temperature - determining their solubility constants – but also the presence of other molecules such as proteins and aminoacids. The biochemistry of LIs in blood is very complex: indeed, they may form very insoluble phosphates, hydroxides, and bicarbonates. They also interact with macromolecules (such as albumin and transferrin) and components of low molecular weight to form soluble complexes [31,42].

A brief survey on toxicity of Gd(III)

The versatility and universality of the calcium signal in biological systems properly reveal the pathological potential of lanthanides in general and gadolinium in particular, as their affinity sequence shows a maximum near the middle of the lanthanide series that is characteristic for calcium-binding sites [33]. All LIs are well suited to block calcium ionic currents across cell membrane through their ability to cross individual single calcium channels, and they can affect calcium currents at micromolar concentrations [33,34]. They are able to directly trigger the release and to inhibit monoamine transporters by interacting with sites of the transporters involved in the amine and Na + binding [35]. LIs can also occupy magnesium sites of macromolecules in a specific manner, particularly in certain Mg^{2+}-requiring enzymes, but there are

also examples of replacement of Fe^{2+} and Fe^{3+} [31]. LIs are able to block the cellular uptake of calcium, and thus they can inhibit the numerous physiological processes which depend upon Ca^{2+} influx [31]. This is of great relevance for the numerous stimulus-coupled cellular responses [31]. Thus, in the nervous and muscle systems "lanthanides block the transmission of nervous impulses, prevent the contraction of smooth, skeletal and cardiac muscle, depress reticuloendotelial function, and inhibit a variety of hormonal responses" [31]. When bound to a Ca^{2+} binding enzyme, LIs often alter the kinetics of the biological process catalyzed by that enzyme [29,31]. Notably, "Gd^{3+} is able to inhibit the activity of some enzymes such as Ca^{2+}-activated Mg-adenosine triphosphatase (ATPase) in the sarcoplasmic reticulum of skeletal muscle fibers, some dehydrogenases, kinases, glutathione S-transferases and aldolase via non-competitive inhibition of Ca^{2+} binding" [28]. In neurons, Gd(III) at a concentration of 100 nM–100 μM can directly trigger the release of neurotransmitters [43]. Gd(III) is also able to affect mammalian cell motility, adherence, and chromatin structure. In vitro experiments have shown the occurrence of chromatin distortion including aggregation, the formation of highly condensed chromatin patches, its stickiness, and its precipitation from 0.75 μM concentration and higher [36]. Gd(III) causes necrosis in liver and spleen, mineral deposits in capillaries (mainly in lungs and kidneys), thrombocytopenia, and prolonged prothrombin time [30,31].

Clinical evidence in support to the hypothesis

Evidence of retention in humans

Numerous contributions to the literature have reported Gd(III)-containing deposits in humans, not just in patients diagnosed for nephrogenic systemic fibrosis (NSF) [44–49] but also in subjects with normal renal function [21,50–55]. Unquestionable evidence of retention has been reported for the bone [56–58], brain, and other tissues involving both the analysis of ex vivo and autoptic specimens [54–61].

Retention of gadolinium in human bone tissue has been demonstrated [56–58] in femoral head of subjects who underwent total hip arthroplasty, and significantly higher deposits were found in patients who received linear agents than macrocyclic ones. Abnormal levels of gadolinium have been found up to 800 times higher than in controls evaluated up to 8 years after the exposition. These data openly demonstrate the potential for the occurrence of long-term retention of gadolinium in bone, even in patients with normal renal function. Moreover, replete and growing MRI data support evidence of retention of gadolinium species in the human brain following intravenous administration of GBCAs [21,62]. A key finding links gadolinium deposits measured in post-mortem neuronal tissue specimens to the hyperintense signal from T1-weighted MR (T1-wMR) images [61]. Increased intensities in specific brain areas (i.e., the dentate nucleus in the cerebellum (DN) and globus pallidus (GP), mainly) on non-CE T1-wMR images have been reported in several studies object of recent review studies, mainly focused on radiological sources [50,52,53]. The clinical significance of all these data and their pathological implications are still debated and remain unclear [21,50]. However, restrictions, warnings, and labeling updates have been issued over the years until to the most recent revisions [26]. Some studies link abnormal data, suggestive of gadolinium deposition, to the molecular structure of the agent and advocate the release from pharmaceutical ligands to linear agents [63–67] but not macrocyclic ones [68–70]. While other studies confirm a role for macrocyclic agents [71], supported by the strongest experimental datum of positive biopsies [55]. Converging data have also been published about the paediatric brain, demonstrating positive correlations to the number of doses [72–75,71,62]. The role of repeated administration appears of major concern [61,70].

Abnormal signals on brain images are not limited to specific regions such as DN and GP but have also been reported in other brain areas [61,66,76,74]. These data suggest widespread accumulation of gadolinium in the brain and raise methodological questions on the reliability of intensity normalization methods to estimate deposit occurrence on radiological images [61]. Autopsy studies further confirmed the presence of gadolinium deposits in several brain structures aside DN [59,61].

Data suggestive for pathological consequences of GBCAs and/or its compound other than NSF

Publications and sparse data from FDA Adverse Reporting System support the hypothesis of pathological consequence of exposure to GBCAs and/or its compounds other than NSF. They report symptoms experienced by subjects exposed to these drugs during their clinical history:

1. A case study of a male patient who performed 61 scans and demonstrated co-occurrence of hyperintensity within the dentate nucleus (DN) in the cerebellum in non-CE T1-wMR images, retention of gadolinium in the skin, and severe joint contractures of unknown aetiology, leading to severe disability [54].
2. Four cases of gadolinium toxicity in women patients with normal renal function who underwent CE-MRI scans for different pathologies, and when examined months or years after administration/s they demonstrated "abnormal and unexpected levels of gadolinium in tissues or 24-hour urine specimens obtained long after GBCA exposure" [77]. Their symptoms included flu-like body aches and paraesthesia, burning and sharp pain affecting the central torso, arms and legs, pain in hands and feet, arthralgia, sharp pins and needles in arm, leg, and central torso, headache, clouded mentation, diminished memory, tightening of the skin, fatigue, subjective muscle weakness, disorientation, nausea and rash. Of relevance, physical signs were completely absent in one patient and were confined to skin alterations in the others [77].
3. A survey of patients with normal renal function, who complain of severe self-reported long-lasting chronic symptoms, following GBCA administrations. Despite several limitations of their report, such as anonymous online question survey, the majority of the responders performed at least one form of gadolinium test that confirmed gadolinium content mainly in urine but also blood, hair, or skin [78]. The most commonly reported symptoms are bone/joint pain and head/neck symptoms (headaches, vision change, and hearing change). Other symptoms include skin changes, flu-like symptoms, generalized whole body symptoms, nausea, vomiting, diarrhoea, and difficulty in breathing [78].
4. FDA Adverse Reporting System (FAERS) reports on post-marketing adverse events in conjunction with exposure to GBCAs in patients with normal renal function both with or without demonstrated gadolinium retention [21]. Strong clustering of ages was not observed and retention was demonstrated in paediatric patients too, whilst persistent adverse events were reported in adult patients only; both linear and macrocyclic agents have been involved, and marked female prevalence was observed. Despite the lack of "consistent phenotypes" and the heterogeneity of adverse events reported, clustering of clinical categories was identified around musculoskeletal, neurological/cognitive, cutaneous, and pain syndromes. FAERS presents five cases in more details: three of them report evidence of gadolinium retention and symptoms, two report just symptoms still without investigated retention but a definite time correlation. All the presented cases are women who received intravenously administration of different types of GBCAs (case 13238462, 2017) (case 11805981, 2015) (case 11755699, 2015) (case 12959507, 2016) (case 12618165, 2016) [96].

Evaluation of the hypothesis

Symptom similarities

Compelling overlapping and similarities can be clearly observed comparing signs and symptoms of FMS and adverse reactions associated with GBCA administrations and/or gadolinium retention [77,78,79]. They span from muscles dysfunctions - neurological in nature - to cognitive impairment: bone/joint pain and head/neck symptoms (headaches, vision change, and hearing change), muscle pain, subjective muscle weakness, chronic fatigue, exercise intolerance and arthralgia, flu-like body aches and paraesthesia, burning and sharp pain in arms, legs, and central torso, pain in hands and feet, sharp pins and needles, tightening of the skin, clouded mentation, diminished memory, disorientation and trouble concentrating. A marked female prevalence is a further common feature among the two conditions. Nevertheless, not only analogies and matching symptoms but also biochemical pieces of evidence provide insight into a role for gadolinium in FM. Indeed, the literature is rich of interesting evidences; nevertheless, most of the times it lacks a comprehensive explanation of the primary cause of the experimental findings at their biochemical foundations. These may be disentangled in the light of biochemistry of gadolinium. A brief analysis, far from being exhaustive, focuses on a sample of data that converge in sustaining the hypothesis.

Neurotransmitters

Neurochemical imbalances in the central nervous system in FM were early hypothesized and investigated as a possible cause underlying FM pathophysiology [80–82]. Several studies focused on the serotonergic system [80,83,84,85], substance P [86,81,87,88,89], glutamate and excitatory amino acids [82,90,91], dopamine [92–94], imbalances of the hypothalamic-pituitary axis (HPA) [95], neuropeptide Y [96], and on inflammation markers and cytokines [84,97–101]. Decreased concentrations of serotonin (5-HT), its precursor tryptophan (TRP), and its metabolite 5- hydroxyindoleacetic acid (5-HIAA) in the serum and/or cerebrospinal fluid (CSF) of FM patients have been variably demonstrated supporting the hypothesis of a “systemic involvement of 5-HT” in FM [81,80,83,84]. Altered amino acid homeostasis [82,102,103] and transporter activity, particularly involving the specific serotonin transporter SERT [104], have also been reported: aside of a decreased expression in cellular membranes, a “deficit in functionality” has been reported, and ascribed by the authors to the observed decrease in transport rate, despite still lacking its underlying causes [104]. Interestingly Gd(III), as the other LIs, can inhibit SERT and the other monoamine neurotransmitter transporters (i.e., noradrenaline transporter (NAT) and dopamine transporter (DAT)) [35]. And indeed, in FM patients alterations have been found regarding not just 5-HT but also dopamine: Wood and colleagues [93] found evidence of dysregulation of dopaminergic neurotransmission, abnormal dopamine response to pain [92], and disruption of presynaptic dopamine activity in brain regions where “dopamine plays a putative role in natural analgesia”. Moreover, other than dopamine, DAT is also known to be involved in neuronal uptake of catecholamines [105]. Once more, Gd(III) has been demonstrated to be a potent blocker of catecholamine release too [38]. Neurotransmitter alterations are also known in the CSF of FM patients: they comprise decreased concentrations of amino acids and their metabolites [106], marked increased concentration of the putative nociceptive neurotransmitter substance P (SP) [87,86,81,88,89], glutamate [91] and also increased nerve growth factor (NGF) concentrations [107]. GBCAs are able to enter into the CSF and brain, and this occurrence is not isolated to well-known pathological states of a compromised blood-brain barrier (BBB) [52,58,61].

Endogenous metal cations and trasmetallation

Deficiency of trace elements and/or alterations of divalent cation concentrations has been early hypothesized to take part in the pathophysiology of FM as well. Some research findings converged in this direction among the years [108–112], despite still lacking to grasp the reason why they occurred [109,110]: significantly decreased serum level of zinc and magnesium has been found in FM patients compared to the healthy controls [109], substantially lower mineral concentrations of calcium, magnesium, copper, and manganese in the hair of female patients with FM [110], intracellular concentration of both calcium and magnesium decreased in FM patients [113], lower levels of total and free serum calcium in patients than in controls [112]. It is known that endogenous divalent cations, but also Fe^{3+}, can be indeed sequestrated by exogenous pharmaceutical ligands in the event of break-down of GBCAs and trasmetallation [27].

I briefly focus on zinc, not to intend that it is the most important deficiency in all FM patients. Animal studies suggest zinc to be a strong competitor for Gd chelators [28]. Zn^{2+} is a fundamental metal cation in the human body to maintain and regulate cellular and subcellular functions of virtually all cells [114]. After iron, it is the “most abundant trace metal in the human body with an average of 2.3 g for a 70-kg adult” [27]. It plays crucial roles in the nervous system, immunity function, and gastrointestinal apparatus [115]. It acts as a cofactor in gene expression and enzymatic reactions involving more than 300 enzymes covering all six classes of enzymes [27,114]. Of relevance its role in the nervous system at presynaptic terminal, co-released with glutamate in the brain, and involved in neuronal excitability and synaptic plasticity, in the regulation of conductivity of voltage-gated-calcium-channels, and calcium signalling [114]. Increased zincuria may be a clue suggestive for in vivo transmetallation following intravenously administration of GBCAs [27–29]. Anyway, zinc deficiency is not always a necessary condition to recognize its occurrence associated with gadolinium retention in patients. The case of chronic zinc poisoning from denture cream published by Greenberg [116] well demonstrates the high potential for transmetallation involving Zn^{2+} in the presence of GBCAs, indeed favoured by the high concentration of zinc and leading to gadolinium retention and release for a long time. This case, moreover, shows the high potential of apparently casual events in patient's history able to interfere with the excretion of GBACs. ‘Border conditions’ (i.e., surrounding physico-chemical conditions) can lead to unexpected pathological outcomes. Moreover, the Gd-containing deposits that have been found in the brain autoptic tumour specimen demonstrate the presence of Zn more frequently than in the NSF cases [60]. Sherry and colleagues [29] bring into focus the impact of transmetallation on zinc in blood.

Inflammation markers: Cytokines and tumour necrosis factor α (TNF-α)

Inflammation markers and cytokines have been variably investigated in FM [97]. Schwartz et al. [84] found an interesting marked increase of serum levels of IL-6 during TRP depletion testing in FM patients than in control subjects. Previous studies investigating the role of IL-6 in the activation of the HPA and on the production, release, and metabolism of 5-HT showed that peripherally administered IL-6 increases both TRP and 5-HIAA concentrations in the brain [84]. IL-6 appears to regulate 5-HT metabolism in FM patients, together with an intriguingly uncoupling of the 5-HT metabolism from TRP availability [84]. More recently, Mendieta and colleagues [98] found an elevated concentration of both IL-6 and IL-8 in peripheral blood of FM patients and positive correlation with clinical scores. And indeed two other studies associate the levels of IL-8 and IL-6 to clinical symptoms in FM [99,100]. Results by Wang et al., instead, only partially agree with above data, as they found elevated serum levels of IL-8 and tumour necrosis factor α (TNF-α), but not IL-6 [101]. By the authors their

results suggest that proinflammatory cytokines IL-8 and TNF-α are involved in FM but "they do not apparently provoke the pain of FM directly" [101]. Again, something seems to be there triggering alterations, but it is still mysterious and apparently invisible.

In vitro experiments may help to disentangle the skein: the effects of GdCl3 on the precipitation of calcium phosphate and the profibrotic activation of macrophages provide converging evidence on a role for gadolinium in FM. In an in vitro cellular model with RAW 264.7 macrophages, increased production of IL-6 and transforming growth factor-β1 (TGF-β1) by $GdCl_3$ has been demonstrated [117]. The effect of $GdCl_3$ involves also precipitation kinetics of calcium phosphate, morphology, composition, and size of precipitates. In vitro data showed the induction of the expression of profibrotic cytokines and growth factor in normal human peripheral blood monocytes directly by Gd(III) from GBCAs: gadolinium "stimulates macrophages to release fibrotic cytokines and growth factors capable of initiating and supporting the issue fibrosis"[117,118]. Despite belonging to minor symptomatology, that definitely does not significantly affect the quality of life of patients, skin-related symptoms have been observed in FM patients such as burning, pruritus, tingling, and increased sweating [119]. Over expression of mastocytes in skin biopsies of FM patients have been found [120] and various changes such as oxidative stress and increased numbers of cytokines and mast cells, particularly IL-1, IL-6 and TNF-α [119,121].

Skin fibroblast activation and proliferation have been demonstrated after the exposure to chelated Gd(III) [122]. Fibrosis induced by GBCAs is well known in subjects affected by NSF: not just skin fibrosis but also extracutaneous fibrosis, flexion contractures of joint, and skin thickening [123]. Free Gd(III) released during transmetallation process can precipitate in vivo forming insoluble complexes with phosphate and hydroxides [28]. Phagocytosis of these complexes has been proposed to depress the reticuloendothelial system and lead to foreign body reactions and fibrosis by inhibiting certain enzymes in the dermis [28].

Muscle

The hypothesis of FM as a muscle disorder gathered initial attention, but it lacks of convincing experimental evidence to ground its aetiology into that of musculoskeletal disease, despite some compelling data have been found [124–126]. They led to conclude that muscle biopsy has no diagnostic significance for FM: muscle morphological changes [127,128] never entered diagnostic criteria [129,130], because histochemical findings appeared not specific for FM and often not statistically significant in the small cohort of subjects involved in the studies [124]. Nevertheless, interesting data can be re-evaluated in the light of biochemistry of Gd.

Muscle abnormalities both structural, functional, or metabolic in nature have been found in FM. Of relevance is the fact that structural abnormalities often correlate with biochemical ones and defective energy production, resulting in muscle dysfunction [126]. Biopsy studies report on muscle fiber degeneration and inflammatory infiltrates, 'moth-eaten' fibers and ragged red fibers, rubber band morphology, decreased capillary numbers and thickened capillary endothelium, abnormal mitochondria, sarcolemmic membrane damage, despite some of them only occasionally present in the samples [127]. Sprott and colleagues found interesting results demonstrating DNA fragmentation in muscle biopsies of FM patients and changes in the size, morphology, and the number of mitochondria in muscle fibres [131]. Signs of mitochondrial alteration (up to striking lack of mitochondria in the sample analysed) and abnormal capillary microcirculation (albeit data on capillary density are not univocal) [128] have been found indicating hypoxia, suggestive for an uneven capillary perfusion and low oxidative capacity [127,128]. Capillary microcirculation has been defined 'compromised' in a controlled investigation of the quadriceps and trapezius muscles of patients with derangements of the capillary endothelium and thickening [126].

Despite referred to brain tissue samples, Gd-containing deposits investigated in autoptic tumour specimens have been found by Xia and colleagues [60] primarily in highly vascular areas, in the wall of the blood vessels, and associated with calcifications. It has been already mentioned that long term retention of Gd(III) can have long term consequences variably affecting the activity of enzymes: particularly, in our context, it may worth to recall its possible action on the Ca^{2+}-activated Mg-adenosine triphosphatase (ATPase) in the sarcoplasmic reticulum of skeletal muscle fibers [28] and the results from in vitro studies that demonstrated "Gd^{3+} competitively inhibits Ca2 + ion binding to the transport sites on purified sarcoplasmic reticulum Ca^{2+}-ATPase" [28]. Impairment in the enzymatic reaction involved in energy production such as the many oxidative phosphorylation enzymes involved in the ATP production necessary for muscle contraction might explain the reduced muscle functionality due to decreased energy production observed in patients and the hypothesized impairment of mitochondrial oxidative phosphorylation and ATP synthesis. Mitochondrial membranes are known to have "high affinities for lanthanides possessing at least two classes of binding sites" and LIs are known to be able to "inhibit the uptake of Ca^{2+} by mitochondria, thereby preventing a number of physiological responses coupled to this process" [31].

Discussion

Experimental pieces of evidence support the hypothesis of impairment at the cellular, intracellular, and systemic level in FM highly compatible with collateral effects associated with the interference of Gd (III) and its pharmaceutical chelates from GBCAs into biochemical pathways in vivo. Dechelation and transmetallation have been recognized crucial events for in vivo toxicity of GBCAs. They manifest not only the well-known toxicity of the lanthanide ion Gd^{3+}, but also the pathological potential carried by free ligands: exogenous ligands can indeed sequestrate endogenous cations forming very stable complexes with ions like zinc, iron, and copper reducing their availability for physiological functions in the body [29].

The hypothesis presented here creates a new link between retention of gadolinium in the body and painful conditions as FM and unexplained chronic widespread pain reported after a trauma, surgery, or medical illness. It breaks the hypothesis of a direct role for a physical injury/trauma per se in favour of an indirect one by the subsequent diagnostic procedures. Thus, I propose a new prefix 'post-gadolinium' or 'post-GBCA' to reflect diagnosis reported having an antecedent administration of GBCAs.

The main message from autoptic, ex vivo, and imaging studies is that the existence of gadolinium deposits in humans following the administration of GBCAs for diagnostic imaging purpose is a reality, and it can persist even for long times after administration [58]. Although several points are still theme for debate and research - such as border conditions under which it occurs, risk factors, speciation, and its clinical significance [21,26,52,50] - the concern backed by these experimental evidence is growing. It is also clear that investigation methods, resolution, sensitivity, and detection limits can underestimate quantification and miss or affect the speciation knowledge [60].

The issue of doses appears a crucial point. It is reasonable to assume a dose-dependent contribution related to the retained dose rather than the mere administered dose (depending by amount per time, number of administrations, time distances among different administrations, total amount, agent (i.e., physico-chemical properties such as molecular structure, charge, etc)) and patient's clearance/retention ability. Co-occurrent drug intake and inflammation might further interfere with proper clearance and excretion, and favour retention [132]. The pathological threshold might be variable among subjects and influenced by both genetic and border conditions, despite it is hard to believe that retention of quite toxic Gd(III) in large amounts may lack any clinical symptomatology at all. It is worth to recall that most GBCAs are

approved at a dose of 0.1 mmol Gd/Kg, but double or triple this dose is used, particularly for MR angiography (MRA) [133].

Therefore, three points may be of concern: the high administered dose at single procedures, the retained dose, and the issue of repeated administrations leading to cumulative retention becoming of concern even when the single stored amount is negligible and/or undetectable. Break-down of GBCAs in vivo results in the release of Gd(III) in the blood stream and its incorporation into tissues [58]. Particularly, LIs are known to have high affinity to hydroxy-apatite minerals [31]. Incorporation in bone after the break-down of GBCAs results in the storage of the high toxic cation Gd3+ for years and its possible delayed release [58], this way thus not just triggering but also sustaining symptoms. Moreover, it has been demonstrated in vitro that hydroxy-apatite ($Ca_{10}(PO_4)_6(OH)_2$) is also able to bind both organic chelate Gd-complexes and free Gd^{3+} [60]. As previously mentioned Gd^{3+} has been found incorporated into bone up to > 800 times in patients exposed to GBCAs than in controls and far longer, being found over 8 years after exposure [58]. The storage for a long time of such a toxic cation in crucial compartments involved in body homeostasis such as indeed bone but also in the brain, carries huge health safety concerns that indeed might get evident in “post-GBCA” FM suffers and chronic widespread pain conditions. Darrah and colleagues attempted a rough evaluation of the retained gadolinium, and they estimated the overwhelming of Gd3 + seems to have been cleared from the body, but still the small fraction stored in the skeleton is hundreds of times than expected [58].

Finally, compelling environmental data demonstrate that contamination of water and soil by GBCAs is regrettably a reality [134–141]. This makes possible a silent risk of penetration of Gd(III) of anthropogenic origin (and its pharmaceutical chelates) into humans and animals through the food chain. Indeed, fortuitous compelling data [58] found a high level of gadolinium, comparable to that in a subject who received GBCA administration, in a control subject that did not receive GBCA administration during his life.

Implications

The great number of diagnostic procedures performed worldwide since 1988 [22] (and even earlier during clinical trials) - both with macrocyclic and even much lesser stable linear agents – might account for the big number of FM suffers today in the population [4]. Any diagnostic procedure involving GBCAs [22] in the clinical history of patients is eligible as a trigger for FM symptomatology and unexplained widespread chronic pain.

If confirmed, this hypothesis would have important outcomes and implications for diagnosis, prevention, and treatment for FM and unexplained widespread chronic pain. The diagnosis must take into greater consideration the patient’s clinical history and investigate for gadolinium retention in the body of patients; an obvious prevention strategy comes by itself just avoiding the trigger. Proper strategies to prevent deposition and accumulation of the culprit must be a research priority to be translated into effective actions in the clinical practice.

The hypothesis presented here might explain the different degrees of symptom severity - variably ranging from mild to extremely severe - related to the stored amount of Gd^{3+} and the condition of so-called ‘spontaneous remission’ that would be compatible with a successful albeit delayed excretion.

GBCAs are powerful diagnostic tools but benefits, risks, and collateral effects – particularly those chronic, painful, and disabling – must be properly weighted. Precise record of time, dose, and agent administered must be a mandatory not just for hospitalized patients. Caution should be particularly used for large and/or repetitive administration in chronic or cancer patients who undergo periodical examinations during follow up but also for procedures involving high doses of GBCA such as for instance CE-MRA. It is crucial to undermining the deceptive message that diagnostic procedures involving GBCAs are free of any risk. Awareness of the potential side effects and adverse reactions from GBCAs should be mandatory for every physicians not just for practicing radiologists. Last but not least, on going therapeutic approaches and research in human beings using gadolinium compounds and nanoparticles [142,143] (and reasonably the most of other lanthanides due to their physico-chemical similarities) should not be allowed without a previous demonstration of effective strategies to prevent and/or solve retention and accumulation of so high toxic ions particularly on long-time windows.

Conclusion

The experimental evidence strongly supports the hypothesis of a role in FM for Gd(III) and its pharmaceutical chelate following in vivo dissociation of GBCAs. If confirmed, implications of this hypothesis could impact diagnosis, prevention, therapeutic approaches, and research on FM and unexplained chronic pain conditions, but also the risk-to-benefit ratio of diagnostic procedures involving GBCAs.

Osteo-articular and musculoskeletal widespread pain historically advocated the managements of FM patients to rheumatology specialists but FM is different from the other rheumatic disorders. The confirmation of the leading role for toxicity (and neuro-toxicity in particular) in FM and unexplained widespread chronic pain would advocate a more profitable management of these patients to toxicology and neurology specialists.

Immediate research route to take appears the collection of clinical data looking for the correlation between fibromyalgia diagnosis and gadolinium retention in the body following exposure to GBCAs.

Author contributions

The author confirms being the sole contributor of this work: developed the hypothesis, researched, wrote the paper, and approved it for publication.

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Declaration of Competing Interest

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