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Editorial

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Editorial

Moving forward together: collaborative landscapes of research in idiopathic inflammatory myopathies and calcinosis

This editorial refers to 'Development of a computed tomography calcium scoring technique for assessing calcinosis distribution, pattern and burden in dermatomyositis', by Briana A. Cervantes *et al.*, 2024;63:58–63.

Calcinosis is a common yet enigmatic complication associated with idiopathic inflammatory myopathies (IIMs), which can be associated with pain, impaired physical function and mobility, infection, adjacent tissue destruction/damage and cosmetic burden which can render a significant impact on health-related quality of life [1, 2]. Calcinosis poses a crucial unmet need in therapeutic management and research in both adult and juvenile IIMs. As a global rare diseases research and advocacy alliance for IIMs, the *International Myositis Assessment and Clinical Studies Group* and *the Myositis International Health and Research Collaborative Alliance (IMACS/MIHRA's)* Calcinosis Scientific Interest Group offers consensus commentary on this carefully constructed milestone study by Cervantes *et al.* [3].

This study is the first to characterize the quantitative and qualitative utility of whole-body CT scanning (wbCT) and provides newly proposed IIM-calcinosis subtypes in juvenile and adult DM (JDM/DM). The study, despite its cross-sectional design, potentially revolutionizes our ability to understand disease pathogenesis as well as to enhance clinical practice, advocacy and continued research for calcinosis. The authors investigate a promising, largely safe, feasible and comprehensive multi-modal objective measure, ultra-low wbCT, to assess calcinosis burden in patients with JDM/DM. Unlike other calcinosis studies, Cervantes *et al.* were able to recruit a significant sample of adults with DM but also a substantial number of children with JDM, in whom calcinosis prevalence is reported between 20% and 40% (range 10–70%) [4–9].

JDM/DM-calcinosis is characteristically a widespread phenomenon for which X-ray and US lack sufficient resolution for the comprehensive assessment of extent and distribution of lesions in viewing fields. Other imaging modalities, such as MRI, are impractical compared with wbCT due to time demands, patient comfort and comorbidities, and cost. Demonstrating remarkably higher sensitivity in calcinosis detection and superior accuracy in body areas where IIM-calcinosis expert physical examination and X-ray resolution may be insufficient, wbCT is a promising objective outcome measure in IIM-calcinosis for clinical trials and practice. Low- or ultralow-dose wbCT radiation emission falls below recommended annual radiation exposure limits, and ultra-low radiation emission is only 7-fold the dose of a single X-ray. Given that calcinosis often affects multiple body areas in patients with JDM/DM, multiple X-rays would surpass the radiation emission from one ultralow-dose wbCT. Low- and ultralow-dose wbCT are widely available on current CT workstations and via software enhancement, respectively, making intermittent serial wbCT reasonable for research or as directed by clinical need.

Furthermore, the capacity of wbCT to characterize shape/cluster, structure, consistency, extent, localization/distribution, adjacent tissue and volumetric burden could potentially inform the understanding of calcinosis development and pathogenesis. Through 3D CT imaging, the investigators were able to confirm and improve upon patterns previously defined on X-ray, while identifying previously unpublished locations. The newly proposed calcinosis sub-types require further validation and will benefit from longitudinal assessment of the natural progression of calcinosis that includes baseline very early, mild and no calcinosis. The wbCT approach will facilitate determining the natural history of calcinosis, including initial formation, etiopathogenesis, severity, chronicity, prognosis, disability and disease sub-typing. Importantly, wbCT offers an imaging modality to identify IIM and SSc controls without evidence of calcinosis: these controls are pivotal comparators in clinical, translational, genetic and biomarker analyses of patients with calcinosis.

Recruiting subjects with previously established calcinosis from a tertiary care centre introduces selection bias as well as conferring little insight on location, patterns and calcium scoring in clinically undetectable, mild or very early calcinosis. Correlations of calcium score with disease duration and chronicity were demonstrated, which provides some insight into wbCT's discrimination, reliability and sensitivity to change in IIM-calcinosis. Utilizing wbCT in longitudinal JDM/DM convenience samples of recently diagnosed subjects with JDM/DM may elucidate key insights into natural history, severity, treatment response, surgical amenity or propensity towards infectious or other complications. This is important for future clinical trial designs of therapies aiming to improve calcinosis outcome.

The multi-modal precision of wbCT provides *IMACS/MIHRA* with opportunities to begin long-awaited investigations such as examining whether the favourable effects of exercise and physiotherapy on inflammation and vascularization in IIMs [10] also play a role in preventing/mitigating the development of

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calcinosis in JDM/DM. Furthermore, these multi-faceted wbCT findings are anticipated to accelerate the *IMACS/MIHRA* consensus addressing classification criteria for severity in IIM- and SSc-calcinosis.

This study also poises *IMACS/MIHRA* for key advocacy opportunities in IIMs and other rare diseases. One such topic is the promotion of cost-effective sub-studies exploring wbCT to assess the responsiveness/prevention of calcinosis within industry-sponsored IIM therapeutic trials and IIM natural history data collection. Another advocacy angle might encourage corporations to improve processing software and ultralow-dose ability on current CT scanners to make these radiation-sparing techniques more widely accessible.

The authors do not comment on the smallest detectable lesion or variations in wbCT protocol or dosing required to detect small-vessel intravascular IIM-calcinosis, and the modified Agatston score is currently unlikely to discern IIM from non-IIM-related vascular calcification without visual-aided assessment. However, multicentre collaborative research on longitudinal cohorts, like those facilitated through *IMACS/MIHRA*, will help elucidate these limitations. *IMACS/MIHRA* consensus on bio-specimen protocols is anticipated to eliminate variation in collection, storage and shipping that can occur across research sites, and to provide high-quality tissue and serum bio-specimen signatures that, correlated with wbCT measures (pattern, extent, distribution, calcium score, etc.), can examine the calcinotic vascular and inflammatory tissue environments.

In this study, wbCT scoring correlated with the subjective measures for Physical Assessment of Calcinosis (though has strikingly low sensitivity), but not with HAQ-Disability Index, Myositis Disease Activity Assessment Tool (MDAAT) and Physician Global Assessment. Subjective measures are important in IIMs. The Mawdsley Calcinosis Questionnaire (MCQ) [1], a patient-reported outcome measure (PROM) developed to assess patient experience of SSc-calcinosis, given the lack of an IIM-calcinosis PROM, was recently validated in DM/JDM-calcinosis [6]. With inherent differences between SSc and IIM-related calcinosis [11] in composition (hydroxyapatite *vs* carbonate-apatite), distribution (discrete/localized *vs* widespread) and etiopathogenesis (hypoxic/traumatic vascular injury *vs* inflammatory perivascular injury), these appear to be divergent diseases with potentially different health-related quality of life and symptom experiences. Thus, dedicated qualitative studies are warranted to inform whether a modified MCQ or a completely new PROM will accurately reflect the patient experience of IIM-related calcinosis *vs* SSc-related calcinosis.

In summary, this study is a significant milestone for calcinosis research, care and advocacy. Its implications extend beyond the immediate scope of DM/JDM, offering opportunities for enhanced collaboration, innovation and improved patient care across various rare diseases. The integration of wbCT in therapeutic trials promises future studies leading to more rapid advancements in calcinosis prevention, management and overall patient well-being.

Data availability

No new data were generated or analysed in support of this research.

Contribution statement

All authors contributed to the development of this consensus statement through an iterative consensus project whereby concepts responsive to the topic were nominated, contested and/or augmented. All authors reviewed and revised drafting of the consensus commentary. All authors endorsed each line of the final draft via a final online consensus exercise.

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