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

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^The International Myositis Assessments and Clinical Studies Group (IMACS) and XX (the preliminary name for the future group growing from IMACS), are a group of basic scientists, clinical researchers (paediatric and adult dermatologists, epidemiologists, geneticists, neurologists, occupational therapists, pathologists, physiotherapists, pulmonologists, and rheumatologists), patient and professional organizations, and medical institutions who join IMACS/XX's cross-collaborative research alliance with the goals of accelerating international clinical trial readiness, global professional and lay education and rare disease advocacy in IIMs. IMACS/XX facilitates investigator-initiated projects, assessment and treatment consensus guidelines, and dedication to IIM-specific trainee career development. The IMACS/XX Calcinosis Scientific Interest Group (SIG) is a multi-project task force whose research is led by members of IMACS, Childhood Arthritis and Rheumatology Research Alliance (CARRA) JDM Working Group, American Academy of Neurology (AAN), American Neurological Association (ANA), International Myositis Society (iMyoS), Rheumatologic Dermatology Society (RDS), Pediatric Dermatology Research Alliance (PeDRA), The Myositis Association (TMA), CureJM, and in concert with SSc organizations (Federation of European Scleroderma Associations (FESCA) and *Scleroderma Clinical Trials Consortium (SCTC)). *IMACS/XX Calcinosis SIG fellows.*

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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 significant impact on health-related quality of life (HRQoL)[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, *IMACS/XX^'s Calcinosis SIG* offers consensus commentary on this carefully constructed milestone study by *Cervantes et al*[3].

This study is the first to characterise the quantitative and qualitative utility of whole-body CT scanning (wbCT) and provides newly proposed IIM-calcinosis subtypes in juvenile and adult dermatomyositis (JDM/DM). The study, despite its cross-sectional design, potentially revolutionizes our ability to understand disease pathogenesis as well as 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 20-40% (range 10-70%)[4-9].

JDM/DM-calcinosis is characteristically a wide-spread phenomenon for which x-ray and ultrasound 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 to 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 seven-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 characterise 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 confers 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 design of therapies aiming to improve calcinosis outcome.

The multi-modal precision of wbCT provides *IMACS/XX* 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 calcinosis in JDM/DM. Further, these multi-faceted wbCT findings are anticipated to accelerate the *IMACS/XX* consensus addressing classification criteria for severity in IIM- and SSc-calcinosis.

This study also poises *IMACS/XX* 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 ultra-low dose ability on current CT scanners to make these radiation-sparing techniques more widely accessible.

The authors don't comment on the smallest detectable lesion nor 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, multi-centre collaborative research on longitudinal cohorts, like those facilitated through *IMACS/XX*, will help elucidate these limitations. *IMACS/XX* 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-DI, 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 versus carbonate-apatite), distribution (discrete/localised versus widespread), and etiopathogenesis (hypoxic/traumatic vascular injury versus inflammatory perivascular injury), these appear to be divergent diseases with potentially different HRQoL 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 versus 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.

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