Non-invasive intradermal imaging of cystine crystals in cystinosis.

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Public Summary:
Importance: Development of noninvasive methodology to reproducibly measure tissue cystine crystal load to assess disease status and guide clinical care in cystinosis, an inherited lysosomal storage disorder characterized by widespread cystine crystal accumulation. Objective: To develop an unbiased and semi-automated imaging methodology to quantify dermal cystine crystal accumulation in patients to correlate with disease status. Design, setting and participants: 101 participants, 70 patients and 31 healthy controls, were enrolled at the University of California, San Diego, Cystinosis Clinics, Rady Children's Hospital, San Diego and at the annual Cystinosis Research Foundation family conference for an ongoing prospective longitudinal cohort study of cystinosis patients with potential yearly follow-up. Exposures: Intradermal reflectance confocal microscopy (RCM) imaging, blood collection via standard venipuncture, medical record collection, and occasional skin punch biopsies. Main Outcomes and Measures: The primary outcome was to establish an automated measure of normalized confocal crystal volume (nCCV) for each subject. Secondary analysis examined the association of nCCV with various clinical indicators to assess nCCV's possible predictive potential. Results: Over 2 years, 57 patients diagnosed with cystinosis (median [range] age: 15.1 yrs [0.8,54]; 41.4% female) were intradermally assessed by RCM. 27 healthy individuals (38.7 yrs [10,85]; 53.1% female) were also imaged providing 37 control images. Automated 2D crystal area quantification revealed that patients had significantly elevated crystal accumulation within the superficial dermis. 3D volumetric analysis of this region was significantly higher in patients compared to healthy controls. Medical outcome data was also collected from patients with infantile cystinosis. nCCV was positively associated with hypothyroidism and stage of chronic kidney disease. Conclusions and Relevance: This study used non-invasive RCM imaging to develop an intradermal cystine crystal quantification method. Results showed that cystinosis patients had increased nCCV compared to healthy controls. Level of patient nCCV correlated with several clinical outcomes suggesting nCCV may be used as a potential new biomarker for cystinosis to monitor long-term disease control and medication compliance.

Scientific Abstract:
IMPORTANCE: Development of noninvasive methodology to reproducibly measure tissue cystine crystal load to assess disease status and guide clinical care in cystinosis, an inherited lysosomal storage disorder characterized by widespread cystine crystal accumulation. OBJECTIVE: To develop an unbiased and semi-automated imaging methodology to quantify dermal cystine crystal accumulation in patients to correlate with disease status. DESIGN, SETTING AND PARTICIPANTS: 101 participants, 70 patients and 31 healthy controls, were enrolled at the University of California, San Diego, Cystinosis Clinics, Rady Children's Hospital, San Diego and at the annual Cystinosis Research Foundation family conference for an ongoing prospective longitudinal cohort study of cystinosis patients with potential yearly follow-up. EXPOSURES: Intradermal reflectance confocal microscopy (RCM) imaging, blood collection via standard venipuncture, medical record collection, and occasional skin punch biopsies. MAIN OUTCOMES AND MEASURES: The primary outcome was to establish an automated measure of normalized confocal crystal volume (nCCV) for each subject. Secondary analysis examined the association of nCCV with various clinical indicators to assess nCCV's possible predictive potential. RESULTS: Over 2 years, 57 patients diagnosed with cystinosis (median [range] age: 15.1 yrs [0.8, 54]; 41.4% female) were intradermally assessed by RCM to produce 84 image stacks. 27 healthy individuals (38.7 yrs [10, 85]; 53.1% female) were also imaged providing 37 control image stacks. Automated 2D crystal area quantification revealed that patients had significantly elevated crystal accumulation within the superficial dermis. 3D volumetric analysis of this region was significantly higher in patients compared to healthy controls (mean [SD]: 1934.0 mum3 [1169.1] for patients vs. 363.1 mum3 [194.3] for controls, P<0.001). Medical outcome data was collected from 43 patients with infantile cystinosis (media [range] age: 11 yrs [0.8, 54]; 51% female). nCCV was positively associated with hypothyroidism (OR = 19.68, 95% CI: [1.60, 242.46], P = 0.02) and stage of chronic kidney disease (slope estimate = 0.53, 95%CI: [0.05, 1.00], P = 0.03). CONCLUSIONS AND RELEVANCE: This study used non-invasive RCM imaging to develop an intradermal cystine crystal quantification method. Results showed that cystinosis patients had

increased nCCV compared to healthy controls. Level of patient nCCV correlated with several clinical outcomes suggesting nCCV may be used as a potential new biomarker for cystinosis to monitor long-term disease control and medication compliance.

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