Geographic variation in calcinosis cutis among patients with systemic sclerosis: a preliminary ecological analysis of water chemistry exposure in two U.S. cohorts

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ABSTRACT

Objective. *Calcinosis cutis is a debilitating complication of systemic sclerosis (SSc) with poorly understood pathogenesis and no effective therapies. Environmental exposures, including drinking water mineral composition, have not been systematically evaluated as contributors to calcinosis risk. We report a preliminary ecological comparison of calcinosis prevalence in two geographically distinct SSc cohorts and examine differences in municipal water fluoridation coverage and water hardness as possible environmental variables.*

Methods. *We compared calcinosis prevalence in 84 SSc patients from Davidson County, Tennessee (Nashville metropolitan area) with 121 SSc patients from Salt Lake County, Utah (Salt Lake City metropolitan area) in a cross-sectional analysis. Water fluoridation status and fluoride concentration data were obtained from the CDC Water Fluoridation Reporting System whereas water hardness data were obtained from the USGS Water Quality Portal. Between-group differences in calcinosis prevalence were assessed using Fisher's exact test and unadjusted odds ratios with 95% confidence intervals.*

Results. *Calcinosis was present in 20 of 84 patients (23.8%) in the Davidson County cohort and 6 of 121 patients (5.0%) in the Salt Lake County cohort (OR 5.93, 95% CI 2.27–15.49, $p<0.001$). Davidson County municipal water systems provide near-universal fluoridation at the EPA-optimal level of 0.70 mg/L (~96% of population on community water systems), with moderate water hardness (mean ~158 mg/L $CaCO_3$). Salt Lake County has partial fluoridation coverage (~52% of population), with substantially higher water hardness (mean ~327 mg/L $CaCO_3$).*

Conclusion. *These data identify a significant difference in calcinosis prevalence between two SSc cohorts that co-vary with differences in municipal water fluoridation coverage. The inverse relationship with water hardness suggests that fluoride exposure, rather than calcium substrate alone, may contribute to the environmental risk for calcinosis in SSc. Prospective patient-level studies incorporating individual water source characterisation and comprehensive clinical covariate adjustment are warranted.*

Introduction

Systemic sclerosis (SSc) is a complex autoimmune connective tissue disease characterised by fibrosis, vasculopathy and immune dysregulation affecting the skin and internal organs. Calcinosis cutis, which is the pathological deposition of insoluble calcium in the dermis and subcutaneous tissue, most commonly affects the hands, particularly the distal phalanges of the thumb and index fingers, which are prone to repetitive trauma (1). Calcinosis is among the most refractory and functionally disabling SSc complications, occurring in an estimated 12-40% of patients depending on the cohort and disease subtype studied (2, 3).

Despite its clinical impact, the pathogenesis of calcinosis in SSc remains incompletely characterised, no pharmacologic therapy has demonstrated consistent efficacy in controlled trials, and epidemiologic risk factors beyond SSc clinical features have rarely been examined. While surgical treatment remains the most effective therapy, prevention is the goal (4).

The environmental exposome (*i.e.*, the totality of environmental exposures encountered over a lifetime) is an important but underexplored dimension of SSc pathobiology. Geographic clustering of SSc incidence and severity has been described in association with silica and solvent exposure, but water chemistry as a potentially modifiable environmental variable has not been studied in relation to calcinosis (5). This represents a significant gap, given the biological plausibility of drinking water mineral composition, particularly fluoride and calcium, as contributors to ectopic soft tissue calcification. The dominant community water fluoridation standard in the United States is 0.70 mg/L, but population-level coverage varies markedly by state and county. Tennessee has approximately 96% fluoridation coverage among community water system users, whereas Utah has approximately 52%; however, fluoridation coverage within Salt Lake County varies by municipal service area (6).

Fluoride is known to accumulate in soft tissues including cardiovascular structures with chronic exposure in experimental models (7). Fluoride-induced cellular toxicity promotes intracellular calcium dysregulation, and animal models of chronic fluoride exposure demonstrate elevated calcium deposition in soft tissues (8). Water fluoridation exposure can potentially disrupt intracellular calcium homeostasis through multiple mechanisms, including inhibition of calcium-ATPase activity, induction of endoplasmic reticulum stress, and promotion of reactive oxygen species that impair cellular calcium efflux (9). In the setting of SSc, where vascular injury, oxidative stress, and impaired cellular repair mechanisms are already present, fluoride-induced perturbation of calcium handling could plausibly lower the threshold for ectopic calcium deposition in vulnerable dermal and subcutaneous tissues.

During clinical observation of two SSc patient cohorts at academic centres in Davidson County, Tennessee, and Salt Lake County, Utah, we noted an apparent difference in calcinosis prevalence that prompted a formal ecological comparison. We report here the results of this comparison along with an analysis of water fluoridation and hardness data for these two counties and discuss the implications for the environmental exposome hypothesis of calcinosis pathogenesis in SSc.

Methods

Patient populations

We identified all patients with confirmed clinical diagnosis of SSc meeting 2013 ACR/EULAR classification criteria who were seen at the SSc clinic at Vanderbilt Health, Davidson County, Tennessee, and at the University of Utah SSc Clinic in Salt Lake County, Utah. Patients were included if they had at least one documented clinical encounter within 2022 and resided in the respective county at the time of clinical assessment. A total of 84 patients were identified from the Davidson County cohort and 121 from the Salt Lake County cohort. Calcinosis cutis was defined as subcutaneous or dermal calcium deposition confirmed by at least one of the following: 1) plain radiographic imaging demonstrating calcified subcutaneous deposits; 2) physician-documented clinical examination findings consistent with calcinosis (firm, white papules or plaques with or without spontaneous extrusion of calcium); or 3) pathologic confirmation on tissue biopsy. This definition is consistent with prior published criteria in SSc cohort studies (10).

Water quality data

Municipal water fluoridation status and fluoride concentration data for Davidson County (Tennessee) and Salt Lake County (Utah) were obtained from the CDC Water Fluoridation Reporting System (WFRS), which compiles water system-level data reported by state fluoridation programs on a biennial basis; 2020 data were used (11). State-level fluoridation coverage statistics (percentage of population on community water systems receiving fluoridated water) were obtained from the CDC 2020 National Water Fluoridation Statistics (11). Water hardness data (mg/L as $CaCO_3$) were obtained from the USGS Water Quality Portal, which aggregates monitoring data from public water supply stations, and supplemented with municipal Consumer Confidence Report (CCR) data for major water utilities in each county (12).

Statistical analysis

Calcinosis prevalence was compared between cohorts using Fisher's exact test, which is appropriate for the analysis of binary outcomes in samples of this size. Unadjusted odds ratios with 95% confidence intervals were calculated using standard 2×2 contingency table methods. The unadjusted OR should be interpreted as a preliminary ecological association only. All analyses were performed using standard statistical software. A two-tailed p-value of less than 0.05 was considered statistically significant.

Ethical considerations

This study was conducted as a retrospective review of existing clinical registry data. Institutional review board approval was obtained at each institution (University of Utah IRB #38705 and Vanderbilt University Medical Centre IRB #1618579).

Results

Cohort characteristics and calcinosis prevalence

Calcinosis was identified in 20 of 84 patients (23.8%) in the Davidson County, Tennessee cohort, compared with 6 of 121 patients (5.0%) in the Salt Lake County, Utah cohort. This difference was statistically significant (Fisher's exact test $p<0.001$). The unadjusted odds ratio for calcinosis in the Davidson County cohort relative to the Salt Lake County cohort was 5.93 (95% CI 2.27–15.49). Summary statistics are presented in Table I.

Water chemistry comparison

Davidson County (Nashville metropolitan area) is served primarily by Metro Nashville Water Services, which delivers fluoridated water at 0.70 mg/L to the great majority of the county popu-

Table I. Calcinosis cutis prevalence and water chemistry characteristics by cohort.

Characteristic	Davidson Co., TN (n=84)	Salt Lake Co., UT (n=121)	*p*-value
Mean age, years (range)	56 (23–81)	53 (23–76)	0.16
Female sex, n (%)	61 (72.6)	91 (75.2)	0.69
Limited cutaneous SSc, n (%)	54 (64.3)	98 (81.0)	0.008
Diffuse cutaneous SSc, n (%)	28 (33.3)	19 (15.7)	0.004
Myositis-overlap, n (%)	2 (2.4)	4 (3.3)	1.00
Mean RP duration, years (range)	14 (1–22)	18 (1–26)	N/A
Mean disease duration, years (range)	16 (1–19)	22 (1–31)	N/A
Current/former smokers, n (%)	4 (4.8)	2 (1.7)	0.41
Calcinosis cutis, n (%)	20 (23.8)	6 (5.0)	<0.001
White race, n (%)	67 (79.8)	111 (91.7)	0.02
Municipal water source	100%	100%	N/A
Municipal water fluoridation	Yes (0.70 mg/L)	Partial (~52% population coverage)	N/A
Water hardness (mg/L $CaCO_3$)	158	327	N/A
Calcinosis OR vs Salt Lake	5.93 (2.27–15.49)	Reference	<0.001

Water fluoridation and hardness data from CDC WFRS 2020 and USGS Water Quality Portal, respectively. OR calculated by Fisher's exact test.
OR: odds ratio; CI: confidence interval; $CaCO_3$: calcium carbonate; TN: Tennessee; UT: Utah.

lation. Countywide fluoridation coverage is estimated to be greater than 95% of the community water system population, consistent with Tennessee's overall state fluoridation rate of approximately 96%, ranking among the highest nationally (CDC rank #5 of 51 jurisdictions) (6). Water hardness in Davidson County averages approximately 158 mg/L as $CaCO_3$, classified as "hard" by USGS criteria (121–180 mg/L) (12).

Salt Lake County is served by several major utilities including Jordan Valley Water Conservancy District, Salt Lake City Public Utilities, and various municipal systems. While the major metropolitan utilities serving the most populous areas of Salt Lake County fluoridate at 0.70 mg/L, overall fluoridation coverage for Utah is approximately 52% of the community water system population (CDC rank #43 of 51 jurisdictions) (6). Of note, Salt Lake County has substantially higher water hardness than Davidson County, averaging approximately 327 mg/L as $CaCO_3$, classified as "very hard" (>180 mg/L). This represents more than twice the calcium mineral load of Davidson County water. We acknowledge water hardness is a county-level average and is not a true control variable.

The inverse relationship between water hardness (higher in Salt Lake County) and calcinosis prevalence (higher in Davidson County) is of interpretive significance, as it effectively controls against a simple hypothesis that elevated dissolved calcium in drinking water drives calcinosis. The inverse relationship between county-level water hardness and calcinosis prevalence argues against a simple ecological association between dissolved calcium concentration and calcinosis prevalence but does not exclude a role for systemic calcium metabolism or other mineral exposures. Table II presents comparative data across the cohorts.

Discussion

In ecological analysis, we observed a nearly six-fold higher prevalence of calcinosis among SSc patients residing in Davidson County, Tennessee, compared with those in Salt Lake County, Utah. While the small sample sizes and absence of patient-level covariate adjustment preclude causal inference, the magnitude and statistical significance of the difference, combined with the observed pattern of water chemistry variation between the two counties, supports further study regarding the role of municipal water fluoridation in calcinosis risk within the SSc environmental exposome.

Notably, several established clinical risk factors for calcinosis were more prevalent in the Salt Lake County cohort than in the Davidson County cohort. Patients in Salt Lake County had longer mean disease duration (22 *vs.* 16 years), longer Raynaud's phenomenon duration (18 *vs.* 14 years), and a substantially greater proportion of limited cutaneous SSc (81% *vs.* 64%), all factors previously associated with increased calcinosis risk. Despite these characteristics, calcinosis prevalence was markedly lower in Salt Lake County (5.0% *vs.* 23.8%). Smoking prevalence was low in both cohorts (1.7% *vs.* 4.8%), making smoking an unlikely explanation for the observed difference. In addition, all patients in both cohorts received municipal water service, reducing potential exposure misclassification from private well use. Although these observations do not eliminate the possibility of confounding by unmeasured variables such as autoantibody status, digital ischemia severity, referral patterns, or socioeconomic factors, the directionality of the available clinical characteristics suggests that disease

Table II. Between-cohort comparison of calcinosis cutis and environmental water chemistry variables.

Variable	Calcinosis+ (n=26)	Calcinosis– (n=179)	Crude OR (95% CI)	*p*-value
Davidson Co. (TN) residence	20 (76.9%)	64 (35.8%)	5.93 (2.27–15.49)	<0.001
Salt Lake Co. (UT) residence	6 (23.1%)	115 (64.2%)	Reference	N/A
Near-universal fluoridation exposure (Davidson Co.)	Present	Mixed	Ecological association	N/A
Water hardness (higher in SLC)	Lower (158 mg/L)	Higher (327 mg/L)	Inverse to calcinosis	N/A

Crude OR for calcinosis comparing Davidson County to Salt Lake County as reference. Water data as described in Methods.
OR: odds ratio; CI: confidence interval.

duration, disease subtype distribution, smoking status, and water source alone are unlikely to account for the nearly six-fold difference in calcinosis prevalence observed between cohorts.

Dissolved calcium load from drinking water is rendered less probable by the observed inverse relationship: Salt Lake County water is more than twice as hard as Davidson County water (327 vs 158 mg/L $CaCO_3$), yet the Salt Lake County cohort had substantially less calcinosis. If bioavailable dietary calcium from water were a primary driver of ectopic cutaneous calcium deposition, the opposite pattern would be expected. This ecological dissociation between water calcium load and calcinosis prevalence is an important negative finding that focuses attention on fluoride as a potentially more discriminating exposure.

The contrast in fluoridation coverage between Davidson County (~96%) and Salt Lake County (~52%) provides a meaningful ecological exposure gradient. This difference in population-level fluoride exposure, operating at the tap over years to decades, represents a plausible cumulative exposure differential that warrants quantification at the individual patient level.

An important implication of these findings relates to the within-Utah variation in fluoridation coverage. Salt Lake County itself contains both heavily fluoridated municipalities (Salt Lake City proper, West Valley City, Sandy) and areas with lower or variable fluoride coverage. Future studies that assign individual fluoride exposure based on patient residential address and utility service area, rather than county-level averages, would permit within-cohort analyses that better isolate the fluoride effect while holding other environmental variables relatively constant. The same approach applies to hardness: areas of Salt Lake County served by wells versus surface water sources show substantial intra-county hardness variation, providing further granularity for patient-level analyses.

Several important limitations of this analysis must be acknowledged. First and foremost, this is an ecological analysis based on aggregate county-level water data rather than individual patient water exposure. Although experimental studies demonstrate fluoride-induced alterations in calcium handling at higher exposure levels, whether these mechanisms occur at concentrations encountered in optimally fluoridated municipal drinking water remains uncertain. Ecological studies are inherently subject to the ecological fallacy, an association observed at the group level does not necessarily hold at the individual level. Second, the cohorts are drawn from academic tertiary-care SSc programs, which may have distinct referral biases and case mixes. Third, individual patient history regarding residential stability, use of bottled water consumption and dietary fluoride sources (tea, fluoride supplements) is not captured in this analysis. Finally, the statistical analysis is limited to unadjusted comparisons; formal logistic regression with covariate adjustment awaits patient-level data collection.

Despite these limitations, we believe this preliminary ecological analysis makes a meaningful contribution to the emerging literature on environmental contributors to SSc complications. To our knowledge, this is the first formal report to examine the relationship between municipal water fluoridation and calcinosis cutis prevalence in SSc. The magnitude of the between-cohort difference and the counterintuitive inverse relationship with water hardness together constitute a hypothesis-generating signal that warrants prospective investigation.

Future studies should incorporate patient-level fluoride exposure assignment and water hardness as a continuous covariate; and fluoride with hardness interaction terms to test whether combined mineral exposure modifies calcinosis risk. Integrated electronic medical records between healthcare systems caring for patients with rare disease may provide an appropriate platform for a prospective environmental exposome investigations by geocode.

Conclusions

We report a significant difference in calcinosis cutis prevalence between two SSc cohorts that co-varies with differences in municipal water fluoridation coverage. Davidson County, Tennessee, which has near-universal water fluoridation (~96% coverage) and moderate water hardness, demonstrated a nearly six-fold higher calcinosis prevalence than Salt Lake County, Utah, which has partial fluoridation coverage (~52%) and very hard water (>327 mg/L $CaCO_3$). The inverse relationship between water hardness and calcinosis prevalence argues against dissolved calcium load as the primary driver of this geographic difference and focuses mechanistic attention on fluoride. These findings support the hypothesis that municipal water fluoridation may be a component of the environmental exposome influencing calcinosis risk in SSc. Prospective patient-level studies with individual fluoride exposure characterisation and comprehensive clinical covariate adjustment are needed to test this hypothesis.

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