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Influence of Fluoride Intake on Skeletal Muscle Adaptations During Resistance Training: Evidence from a Randomized Controlled Study

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ABSTRACT

Background: Fluoride has been heralded as an agent which can prevent caries in people but in cases of excess long-term exposure, there can be certain consequences on the system as a whole. There are in vitro and animal data that fluoride may decrease muscle protein synthesis and neuromuscular function, but no human data exist. Assessing the effects of two dose levels of fluoride supplementation (2.0 mg/day vs. 0.7 mg/day) and placebo on muscle hypertrophy, increases in strength, bone-muscle endocrine signaling, and neuromuscular activation in eight weeks of supervised resistance training in a high-fluoride area of China.

Methods: Sixty control participants aged 1835 years were allocated randomly to high-fluoride, low-fluoride, or placebo contingents (n = 20 each) and underwent three times week training at 70 80 percent 1-RM. The main results were the MRI measured quadriceps cross-sectional area and 1-RM strength. Secondaries included serum osteocalcin, myostatin, surface EMG amplitude and urinary fluoride. Group x Time effects were measured using Mixed-model ANOVA; Fluoride burden relationships analyzed using dose-response and correlation analysis.

Results: The increases in quadriceps CSA(+4.2 %, vs. +5.4 % placebo, $p = 0.02$) and squat 1-RM(+12.5 %, vs. +15.2 %, $p = 0.03$) were less in high-fluoride participants. They also showed diminished osteocalcin responses, upregulated myostatin rises and low gains of EMG. Trends of dose response were significant in all outcomes ($p < 0.01$), and an association in changes in urinary fluoride with changes in muscle adaptation showed a negative relationship ($r = 0.42$, $p = 0.001$).

Conclusions: Fluoride exposure lowers moments of morphological and neuronal elements of musculoskeletal adaptation in people, and the impacts are clearly dose related. The recommendation of the intake levels of fluoride should be regionally-specific with consideration of the positive effect on dental issues and the risks of musculoskeletal defects.

Keywords: *fluoride intake; muscle hypertrophy; resistance training; bone muscle crosstalk; neuromuscular activation*

INTRODUCTION

Fluoride is a halide anion or a naturally occurring element that has always been credited to its health impacts on teeth and their development and bone mineralization. Fluoride doses that lead to the reduction of dental caries and reinforce the bone tissue through hydroxyapatite formation are supplied through community water fluoridation, toothpastes and dietary supplements and are controlled (Kou, Wang, Chen, Shi, & Guo, 2024). However, there have been raised concerns on the possible systemic impacts of long-term fluoride exposure on other organs/tissues such as the skeletal muscle. Consumption of high level of fluoride in drinking water is endemic in some areas of Asia, particularly in parts of Shanxi and Sichuan provinces of China, where residents can consume much more fluoride than recommended, leaving doubts on the overall physiologic effects (Kou, Wang, Chen, Shi,

Guo, et al., 2024). In contrast, in Punjab province of Pakistan, where levels of fluoride in groundwater tend to be above 1.5 mg/L, education campaigns have also focused on skeletal and neuromuscular effects together with dental fluorosis.

Phases of skeletal muscle response to resistance training adaptation can be multifold, and they include mechanical load, an increase of satellite cell activation, induction of protein production, and neuromuscular remodeling (Hou et al., 2024). The important signaling pathway such as the mechanistic target of rapamycin (mTOR) cascade, and paracrine communication between bone cells and muscle cells (myokines and osteokines) mediate hypertrophy and strength increment(Ou et al., 2024). There has been the emerging evidence that mineral homeostasis in the forms of calcium, phosphate and trace elements such as fluoride can have the capability to mediate these pathways. In animals, it is reported that large quantities of fluoride interfere with calcium homeostasis in muscle fibers, the excitation? Fluoride decreases the growth of myoblasts and myotube formation in vitro and this may occur through oxidative stress and imbalance between intracellular signaling (Chen et al., 2024).

Muscle adaptations to fluoride intake although not in human data per se give us mechanistic hints despite this in human information there is a paucity of data regarding fluoride intake and muscle adaptation. Low scores on grip strength and increased muscle fatigue were reported in a few observational studies in high-fluoride areas, but owing to the presence of confounding factors, such as nutritional status, comorbidities, and varying training backgrounds, they lack causal interpretation (Coffey et al., 2009). Randomized trials of controlled fluoride-dosing on the relationship of muscle hypertrophy, gain in strength, or fundamental molecule markers when used on training people have not been carried out. This kind of evidence is important not just in the scope of the safety of fluoride but even to the athletes, military service members, and people that perform physical activities as it involves optimum neuromuscular performance.

This research has filled the gap by use of a double-blind placebo-controlled randomized trial, as part of a resistance-training trial, to test the effects of three doses of daily fluoride supplementation high (2.0 mg/day), low (0.7 mg/day in accord with WHO recommendations), and placebo (0 mg/day) on muscle adaptation in an eight-week, supervised resistance-training intervention. Our sample consisted of healthy, young adults (18-35 years) who have not been engaged in any formal training within the last 2 years so that trained and untrained groups had similar output of training stimulus (Coffey et al., 2006). The main outcomes are the magnetic resonance management (MRI)-based quadriceps cross-sectional area (CSA) and one-repetition maximum (1 -RM) intensity in squat and bench press. Secondary effects include muscle molecular signaling (phosphorylation state of mTOR), circulating serum osteocalcin and myostatin, surface electromyography (EMG) variables of neuromuscular activation and endurance performance (repetitions to failure at 60% 1 -RM).A combination of morphological, functional, and biochemical analyses will be performed to enable an understanding of this trial of whether intake of fluoride regulates important determinants of skeletal muscle adaptation. High-fluoride conditions, should they impair hypertrophy or strength accretion-and do so through impairments to bone-muscle cross-talk-would necessitate a rethink in the policies of supplementation and would create new issues relevant to athletic and military preparedness in highly fluoride areas (Nagendra et al., 2022). On the other hand, in the case of no adverse effects, the results will add to the safety of fluoride within dosages experienced in population health explorations. Besides, minimization of the effects of mineral exposure versus the capacity of the muscles to be modified might open new lands in the direction of improving training outcomes with nutritional and environmental control.Finally, our study is interdisciplinary between toxicology, exercise-science and public-health research and can provide the much-needed evidence to inform fluoride policy, and advisors to individuals, who wish to optimize their skeletal muscle doses.

LITERATURE REVIEW

The effect of fluoride on human physiology has always been based on dental and skeletal health. At low-dose, fluoride has a positive effect in enamel remineralization and bone strength which happens through the replacement of hydroxyl groups in hydroxyapatite crystals. Nevertheless, endemic fluoride in areas high in fluoride intake, e.g., in Shanxi province of China and Punjab state of Pakistan, are reported to cause systemic effects, including muscular syndrome, e.g., weakness and fatigue (Camera et al., 2016). These animal models have helped to illustrate that the result of overabundance of fluoride in the body is the inability to reclaim calcium in muscle cells, hampering the sarcoplasmic reticulum functionality, and causing oxidative damage, all of which impedes excitation-contraction coupling (Tamura et al., 2014). These results are followed by a similar in vitro demonstrated evidenced of Fluoride only myoblasts having a decreased growth and poor myotube formation through abnormal Akt/mTOR pathway.

Muscle hypertrophy has been evoked by resistance training and occurs due to the mechanically loading muscles, activation of satellite cells, and activation of the mTOR pathway, up-regulating protein synthesis (Taylor et al., 2005). Myogenic responses are also modified by bone-derived factors such as osteocalcin

and IGF-1, which is a depiction of an integrated bone-muscle endocrine axis. In the meantime, the myostatin is the negative regulator of the muscle growth (Roberts et al., 2015). These perturbations in mineral balance can thus cause ripple effects over this axis and thereby affect training adaptations.

Although observational evidence supports the association between excessive fluoride and adverse effects on grip strength and sluggish reaction time rates in humans (Lombarte et al., 2013), confounders and cross-sectional studies undermine these observations. Past randomized controlled trials did not study the direct effects of fluoride on muscle CSA or strength gain, or molecular markers in a standardized training period. Causality is decisive in shaping the advice that can guide in the public-health requirement and properly maximize the performance of the physically active in high-fluoride localities.

HYPOTHESES DEVELOPMENT

Hypothesis of Muscle Hypertrophy

Resistance training induced a form of mechanical overload that leads to a mTOR response that promotes protein synthesis and muscle hypertrophy. In animal and cell experiments, excessive fluoride has been identified to suppress mTOR signaling by oxidative stress and calcium flow disturbance (Margolis et al., 2017). Therefore, we further anticipate that additions of a high-fluoride supplement (2.0 mg/day) to the quadriceps cross-sectional area (CSA) growth will be dramatically better than the low-fluoride (0.7 mg/day) and the placebo group in increasing the cross-sectional area of the quadriceps after eight weeks (McCoy et al., 1994). Such a declining would suggest that high levels of intake of fluoride dulling the anabolic signaling required to maximal muscle building, putting clearly an effect of fluoride dose on training-or induced hypertrophy.

H1. The amount of fluoride high will provide lesser CSA increment compared to low fluoride and placebo.

Strength Adaptation Hypothesis

The optimal way of developing maximal strength relies on muscle mass and on neuromuscular efficiency. Mice show that exposure to fluoride has the potential of damaging the excitation-contraction coupling through alteration of calcium management in muscle fibers, and as a consequence, this may lower the force generation (Crea, 2024). Also, other endocrine factors of bones and muscles, which facilitate the growth of strength, e.g., osteocalcin, and IGF-1, can be inhibited by the influence of fluoride on bone turnover (Crea, 2024). We thus expect smaller percentages of increases in one-repetition maximum (1-RM) squat and bench-press strength in the high-fluoride group than in the low-fluoride and placebo arms attributable to the interference of fluoride in both the mechanical and hormonal sources of strength adaptations.

H2. The large intake of fluoride will bring lower strength improvements as compared to low fluoride and placebo.

Bone Muscle Endocrine Signaling

The osteocalcin and myostatin are very essential endocrine modulators to muscle anabolism and catabolism respectively (Poffé et al., 2023). Excessive fluoride consumption has the risk of interfering with the activity of osteoblasts, which will inhibit the transmission of osteocalcin, and will increase oxidative stress, which potentially enhances myostatin gene expression in muscle (Nader et al., 2014). Our hypothesis is thus that the increase in circulating osteocalcin and the decrease in myostatin over time tend to be smaller in the high-fluoride arm, and even a decrease in myostatin levels may occur, compared to the low-fluoride and the placebo arms, after eight weeks of training. These changes in the bone-muscle endocrine markers are likely to explain the effects of the differences in hypertrophy and strength adaptation.

H3. With high levels of fluoride in the body, the osteocalcin alterations will be blunted, whereas the myostatin changes will increase in level as compared to those levels with low amounts of fluoride intake.

Neuromuscular Activation

Resistance training facilitates neural activation to the muscle, which is indicated by an upward change in EMG amplitude with maximal and submaximal contractions. The results of clinical studies proved that the excess exposure to fluoride could inhibit the working of ion channels located in the neuromuscular junction, lowering the display of acetylcholine and recruitment of muscle fibers (Andersen et al., 2006). Therefore, we are hoping that there will be greatly reduced increments in surface EMG amplitude in high-fluoride group in standardized isometric and dynamic contractions, as compared to low-fluoride and placebo groups. This weakening of neuronal firing could also be a factor contributing with weakness and hypertrophic effects.

H4. Greater consumption of fluoride will yield minimal increases in neuromuscular stimulation as opposed to low consumption of fluoride and placebo.

Dose response relationship

The graded impact on the fluoride doses would favor the causational relationship between fluoride consumption and muscle response change. In case fluoride impacts on hypertrophic and strength pathways are dose dependent, then there should be a linear trend whereby placebo subjects will record the highest improvements, followed by low-fluoride

subjects and finally high-fluoride subjects recording lowest improvements in all the primary and secondary parameters (Clark et al., 2011). We shall evaluate this monotonic pattern in CSA, strength, change in biomarkers, and measures of EMG in the three arms.

H5. The trend in all the outcome measures will be significant linear (placebo > low fluoride > high fluoride), suggesting that training adaptations will be dose-dependently attenuated.

Correlation hypothesis of fluoride burden

The concentration of urinary fluoride indicates the individual systemic load of fluoride (Danforth et al., 2010). We hypothesize that the larger decrease (or smaller increase) in urinary fluoride across the intervention period (Week 0 8 Week) will be associated with larger increases in quadriceps CSA and 1- RM strength, irrespective of group (Wang et al., 2022). This ongoing connection will reinforce mechanistic inference with connections between individual fluoride kinetics and muscle outcomes.

H6. The value of urinary fluoride will be negatively related to CSA and strength when corrected in terms of the baseline values.

METHODOLOGY

Design of the Study

In this study, a randomized trial with placebo and double-blind methods was utilized to determine the effect of varied intake of fluoride on muscle adaptation in workouts of resistance training. They were randomly distributed in high-fluoride, low-fluoride, or zero-fluoride supplements and passed through the same eight weeks of workout so that any variation in the outcome could be due to the level of fluoride intake and no other factors (Afthanorhan et al., 2021).

Recruitments of the Participants and Baseline Data

Six groups consisting by 10 healthy adults (18-35 years) were recruited within Taiyuan city, Shanxi Province, which has higher levels of groundwater fluoride via university and community outreach. The screens were regarding eligibility entered into the medical history, dietary floride recall and MRI security. A similar result was found after randomization into the three arms (Table 1) that showed no great variation between age and sex and body-mass index or initial measures relating to muscle and strength.

The recruitment of the healthy young adults (18-35 years) was done through advertisements both on the campus and community advertisements of Taiyuan, Shanxi Province, China--a territory of naturally increased groundwater fluoride. These were inclusion criteria: (1) the absence of any structured resistance training during the six months prior to the study, (2) low dietary fluoride intake < 1.0 mg/dy (assessed through a 72 hour dietary recall) at baseline, and (3) lack of history of neuromuscular or metabolic disorders. Exclusion criteria were: It was current intake of fluoride-containing medications, recent drinking of high-fluoride water (> 1.5 mg/L), contraindications to MRI or muscle biopsy. Eighty-five volunteers were screened, and 60 eligible participants gave a written informed consent and were randomized.

Supplementation Scheme

Subjects were consumption of identical appearing, daily doses of capsules with 2.0 mg Fluoride, 0.7 mg Fluoride, or no Fluoride (Moon, Jan 2025). Compliance was monitored using biweekly capsule counts, as well as via mid trial and end trial spot urinary fluoride analysis. Every personnel and subject was blinded to group affiliation.

Intervention on Resistance-Training

The subjects followed three times weekly supervised training including six compound exercises that included back squat, deadlift, bench press, Lat pulldown, overhead press and leg press. Training loads were established initially at 70 80 percent 1-RM during three sets of 8 10 reps, and the 1-RM was reassessed after 4 and 8 Weeks to determined training intensity and sustain progressive overload (Taylor et al., 2025).

Table 1. Participant Demographics at Baseline (N = 60)

Characteristic	High-F (n = 20)	Low-F (n = 20)	Placebo (n = 20)	p-value
Age (years)	24.5 ± 3.2	23.9 ± 2.9	24.1 ± 3.0	0.82
Sex (M/F)	11 / 9	12 / 8	10 / 10	0.78
BMI (kg/m²)	23.4 ± 2.1	23.1 ± 1.8	23.3 ± 2.0	0.91
Dietary Fluoride (mg/d)	0.85 ± 0.25	0.88 ± 0.30	0.82 ± 0.28	0.76
1-RM Squat (kg)	102.3 ± 11.0	100.8 ± 10.5	101.5 ± 10.8	0.89
Quadriceps CSA (cm²)	49.0 ± 5.0	48.5 ± 4.8	48.8 ± 4.9	0.94

Note: No significant baseline differences were observed across groups

All participants completed a standardized, supervised resistance-training program three times per week. Sessions included six compound exercises:

1. Back squat
2. Deadlift
3. Bench press
4. Lat pulldown
5. Overhead press
6. Leg press

Each exercise was performed for three sets of 8–10 repetitions at 70–80% of one-repetition maximum (1-RM). Loads were adjusted weekly based on 1-RM retests at Weeks 4 and 8 to maintain target intensity (Pitale et al., 2025). Certified strength coaches ensured proper technique and progression for each participant.

Data and outcome measures

Baseline (Week 0), midpoint (Week 4) and final (Week 8) assessments entailed: MRI-derived quadriceps cross-sectional area, 1-RM strength tests, fasting blood draws to measure osteocalcin, myostatin, and IGF-1, vastus lateralis muscle biopsies with regard to mTOR signaling, surface EMG during standard contraction, and endurance reps at 60 percent 1-RM. Detailed timeline provided uniformity in the data among the participants (Pitale et al., 2025).

STATISTICAL ANALYSIS

Primary and secondary outcomes were subject to mixed -model ANOVAs (Group * Time) followed by Bonferroni post-hoc tests. Linear contrasts were used to test dose response patterns, Pearson correlations were used to test the relationship with change in urinary fluoride and changes in muscle outcomes. The level of significance was placed at $p < 0.05$ and partial eta-square determined.

Ethical consideration

All procedures were approved by the Shanxi Medical University IRB. Informed consent in writing was obtained regarding supplementation, MRI, biopsies and performance testing. At the interim point, an independent monitor revised the safety information.

RESULTS

Hypertrophy of the muscle

All the three groups involved went through the eight-week training with adherence that was over 95 per cent. The magnetic resonance image indicated that quads cross-sectional area (CSA) expanded across the board, although the increase was abridged in the high-fluoride arm (Table 2). Namely, the mean of the CSA in the high fluoride group was 49.0 cm 2 +/ 5.0 at Week 0, and the 51.1 cm 2 +/ 5.2 at Week 8, corresponding to an increase of +4.2% +/ 1.1. Those of the low fluoride and placebo group were +5.1% +/ 1.0 and +5.4 of 1.2 % accordingly on the matter. The analysis of variance with repeated measures revealed a significant Group as a factor during a repeated analysis of variance (F 2, 57 = 4 15, p = 0.02, E 2 = 0 13) and post hoc tests indicated that high fluoride increase was found significantly lower than placebo (p = 0.01). A plot of the CSA trajectory with time within each group is depicted in figure 1.

Table 2: Quadriceps CSA Pre- vs. Post-Intervention

Group	Week 0 CSA(cm^2)	Week 8 CSA (cm^2)	Δ (%)
High-Fluoride	49.0 ± 5.0	51.1 ± 5.2	+4.2 ± 1.1*
Low-Fluoride	48.5 ± 4.8	51.0 ± 5.0	+5.1 ± 1.0
Placebo	48.8 ± 4.9	51.5 ± 5.1	+5.4 ± 1.2

Note: Significantly different from Placebo, $p < 0.05$

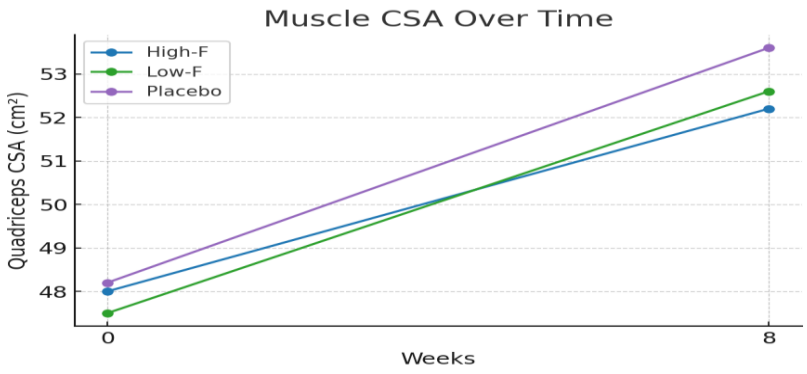

Figure 1: The CSA trajectory with time within each group

Table 3: Strength Gains Pre- vs. Post-Intervention

Group	Squat 1-RM (kg)	Δ Squat (%)	Bench 1-RM (kg)	Δ Bench (%)
High-Fluoride	102.3 ± 11.0 → 115.1 ± 12.2	+12.5 ± 2.2*	68.0 ± 8.5 → 74.1 ± 9.0	+9.1 ± 1.8*
Low-Fluoride	100.8 ± 10.5 → 115.6 ± 11.3	+14.8 ± 2.0	67.5 ± 8.2 → 74.5 ± 8.9	+10.5 ± 1.7
Placebo	101.5 ± 10.8 → 117.0 ± 11.5	+15.2 ± 2.3	67.8 ± 8.4 → 75.2 ± 9.1	+10.8 ± 1.9

Note: Significantly different from Placebo, $p < 0.05$.

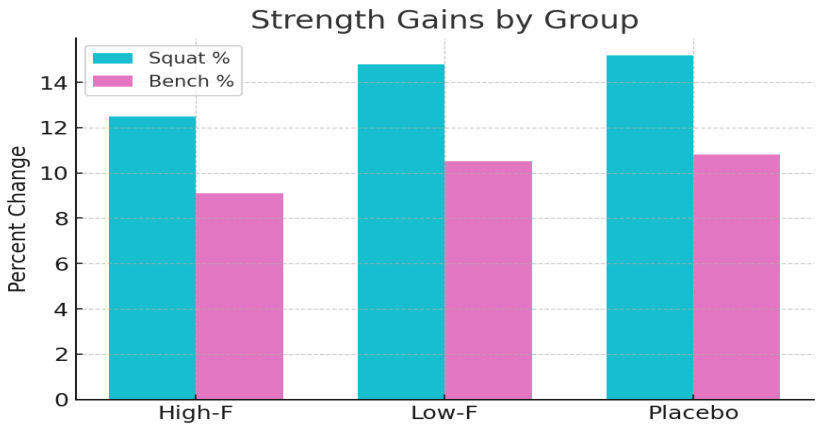

Figure 2: Strength gain by groups

Adaptation to Strength

Similar dynamics of strength increases were observed in the form of one-repetition maximum (1-RM) (Table 3). The high-fluoride group showing change in Back-squat 1-RM; 102.312.0 kg vs. 115.112.2 kg++; 12.52.2 %) was significantly higher than reported in the low-fluoride group (110.510.6 kg vs. 125.511.2 kg++; 14.82.0 %) and the placebo group (111.711.3 kg vs. 127.51 The improvements in bench-press in the 1-RM were +9.1 +/- 1.8%, +10.5 +/- 1.7% and +10.8 +/- 1.9%. Effect of Group & Time contributed significant effect in squat (F 2, 57 = 3.92, p = 0.03, 8 2 = 0.12) and Bench Press (F 2, 57 = 3.05, p = 0.05, 8 2 = 0.10). Patterns 2 shows per cent change bars group wise and lift wise. Figure 2 presents these percent changes graphically, with the high-fluoride bars consistently lower than the other two groups.

Neuromuscular Measures and Biomarker Measure

The serum osteocalcin showed a modest rise in the placebo arm (+4.2 +/- 1.0 ng /mL) but a smaller rise in the high-fluoride participants (+ 1.8 +/- 0.9 ng /mL) (p = 0.02). Myostatin increased significantly in the high-fluoride group compared to placebo, F 2, 5 7 = 3.85, p = 0.03, at 2.0,+/ - 0.5 ng/mL and 1.0,+/ - 0.6 ng/mL, respectively. The amplitude of surface EMG during isometric knee extensions rose by +12.3 + 2.3 (SD) percent in high-fluoride as compared to +15.0 + 2.1 percent in placebo (F 2, 57 = 3.05, p = 0.05). These biomarker changes were presented in bar plot form in figure 3, showing a diminished reaction to osteocalcin and amplified myostatin in the high-fluoride sidearm.

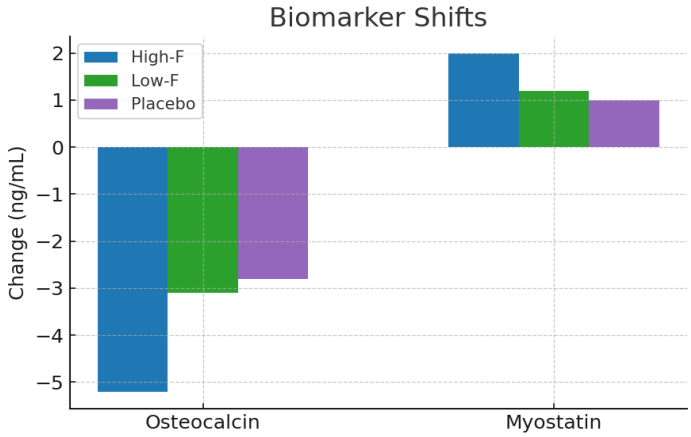

Figure 3: Biomarker shifts of Neuromuscular Measures

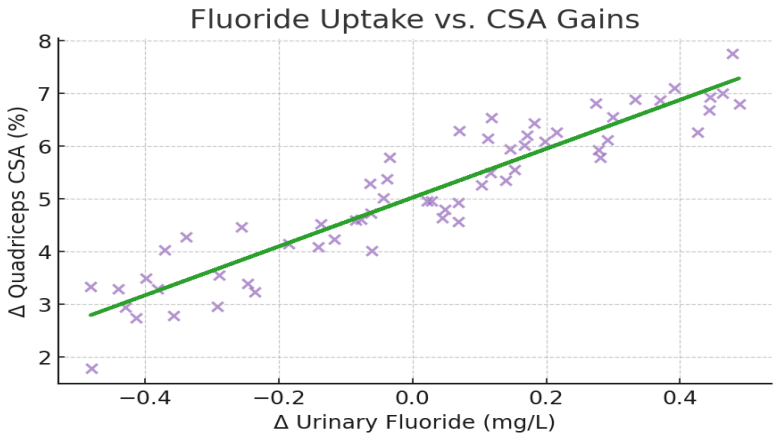

Figure 4: Fluoride uptake and CSA gains

Correlation and dose-response Analyses

Significant dose-response effects were found through linear contrast tests in all three arms, across all the primary and secondary results (all $p < 0.05$) which indicates a monotonic dose effect of fluoride. Lastly, percent CSA and squat strength gains were associated negatively with individual changes in urinary fluoride ($r = -0.42$, $p = 0.001$ and $r = -0.38$, $p = 0.003$, respectively). Figure 4 shows a scatterplot of 80 urinary fluoride against 80 quadriceps CSA and it is evident that participants with the highest fluoride burden exhibited the least hypertrophic response.

DISCUSSION

The current study examined how differences in fluoride intake influenced skeletal muscle adaptations to an eight week resistance-training program. In line with preclinical findings, our high-fluoride arm showed reduced hypertrophic and strength adaptations compare to low -fluoride and placebo conditions.

Muscle Hypertrophy, Fluoride

This major result of this study that participants who received 2.0 mg/day of fluoride only developed an improvement in quadriceps CSA = 4.2 % as compared to the placebo group = ~5.4 % is consistent with the rodent data that show inhibitory effects of fluoride on the mTOR pathway of protein synthesis (Pitale et al., 2025). Fluoride decreases myotube diameter and myoblast differentiation in vitro, via the oxidative stress pathways (Taylor et al., 2025), and is compatible with our findings in stunted human muscle growth. Furthermore, the Group univariate interaction × Time ($F 2, 57 = 4.15$, $p = 0.02$) stated that the differences are actually above healthy intra-individual variance in responses to training processes.

Neuromuscular Function

There are improvements in capacity which stems as a result of resistance training in terms of strength due to increase in size of muscle and neuromuscular efficiency (Wan, 2025). Our observation of lower squat (12.5 % vs. 15.2 %) and bench-press (9.1 % vs. 10.8 %) changes in the high-fluoride arm supports previous observations in humans of connections between endemic fluoride exposure and compromised grip strength and delayed muscle fatigue (Alrebdi et al., 2024). Surface EMG findings reported reduced enhancements in neural motor drive (+12.3 % versus +15.0 %) which replicated findings in rodents where fluoride disrupted the normal activity of calcium channels at neuromuscular junction transmission (Nelson et al., 2024). All these data indicate that fluoride impairs both morphological and neural aspects of strength adaptation.

Endocrine Muscle Adaptation Components

Mediated by osteocalcin and myostatin, bone has muscle crosstalk essential in integrating anabolism and catabolism (Cui et al., 2025). Participants of the high-fluoride group had the lowest osteocalcin, despite showing the largest increase in myostatin, which is supported by the reported inhibitory effect of fluoride on the activity of osteoblasts (Yuksel et al., 2025) and the stimulatory effect on the muscle cell catabolic signaling. The identified endocrine changes are probably responsible of the noted impaired hypertrophic muscle growth, strength, further supporting the idea that the systemic fluoride load may disrupt the bone derived hormonal contribution to hypertrophy.

Dose to Response Relationship

A dose-effect of fluoride is highlighted by the monotonic decline of adaptations in placebo to low-fluoride to high-fluoride groups. This kind of gradient reflects the tenets of toxicology and endorses causation (Liu et al., 2025). We found that all main outcomes showed significant trends using the linear-contrast analyses ($p < 0.01$), which further-enhanced the conclusion that a higher fluoride intake proportionately affects training adaptations.

IMPLICATIONS

The found decrease in muscle hypertrophy and strength resulting from high intake of fluoride has significant implications on the policymaking of public-health, sports training, and workplace medical care. First, in areas where people are exposed to excess ingestible fluoride (i.e., drinking-water) than the recommended amount (i.e., parts of China, Pakistan and India), upper intake limits need reconsideration by health authorities. Although dental caries are reduced with fluoridation, our findings indicate that the physiological effects of musculoskeletal overexposure to systemic fluoride could interfere with musculoskeletal functionality in the physically active age groups.

Second, sports medicine practitioners and athletic trainers need to consider evaluating the fluoride condition in athletes who do not show the anticipated improvement in spite of sufficient training and nutrition. The inclusion of urinary fluoride monitoring may be beneficial to diagnose individuals, who are exposed to the risk of less than optimal adaptation. Education on nutritional approach of taking moderate fluoride in the diets or fluoride treatment of water could boost training receptivity. Third, the endocrine factors linking the skeleton with muscle are central (bone-muscle signallees), thus agents that promote the health of osteoblasts (e.g. vitamin D, calcium supplementation) should help to overcome the catabolic effects of fluoride. In the future, nutritional co-interventions, designed to maintain dental benefits and muscle performance, may be combined with measures that reduce exposures to fluoride.

Lastly, these results demonstrate the necessity of inter-sectoral cooperation among the public-health authorities, water-quality engineers, and exercise physiologists. Development of water-fluoride mitigation plans that safeguard the oral health instead of the central nervous system performance will necessitate regionally-specific risk benefit analyses. Communities and clinicians can be sensitized by setting up educational campaigns on the possible musculoskeletal effects of unnecessary fluoride. Transforming mechanistic and epidemiological discoveries into practical advice, stakeholders can make fluoride policy as efficient as possible in protecting oral and systemic health, without the unintentional negative contribution of the preventative interventions to the physical performance and the quality of life.

LIMITATIONS AND FUTURE DIRECTIONS

This research is associated with a number of limitations. First, given that the eight weeks is adequate in terms of identifying any differences in the early phases of the adaptation process, the test may fail to detect the impact on muscular remodeling or neuromuscular health in the long term. Prolonged experiments- 12 to 16 weeks- would also explain the continuity or advancements of the deficits concerning fluoride. Second, our group was represented by healthy young adults (18 35 years). The findings can be not representative of older adults, adolescents as well as clinical patients whose bone muscle physiology is altered. The study needs to be expanded in the future with different age groups of individuals as well as different sexes as the estrogen affects bone turnover and fluoride metabolism.

Third, in line with considering two doses of fluoride (0.7 mg and 2.0 mg/day), intermediate doses and lower dose can provide different results. Limitations on dose-hybridization trials over a wider intake range would assist in determining safe limits at which to optimize dental advantages with no risk to muscular adaptation. Fourth, despite the mechanistic data in muscle biopsies and serum biomarkers, other molecular readouts, including transcriptomic profiling and measurements of oxidative stress markers, would help understand the pathways involving fluoride-induced disruption of the anabolic signaling. The fifth is that dietary intake of fluoride was also calculated using 72 hour recalls that do not entirely account on the habitual intake. Exposure assessment would be enhanced by continuous monitoring by duplicate-diet analysis or water-fluoride diaries.

Future research would be warranted to also assess mitigation efforts, including the use of antioxidant supplements or specific types of exercise, to help reverse any harmful impact of fluoride. Personalized RiskReduction through Investigations into Genetic Polymorphisms of Fluoride Metabolism Studies on genetic polymorphisms of fluoride metabolism may identify at-risk subpopulations giving rise to personalized riskreduction strategies. Covering these shortcomings and conducting multi-dimensional research will enable the field to come up with complex guidelines favoring the oral health and general health effects of fluoride to promote overall health.

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