Pharmacokinetics of fluoride in human adults: The effect of exercise

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HIGHLIGHTS

- This human study adds to understanding of the effects of exercise on fluoride (F) metabolism.
- F pharmacokinetics following no, light, moderate and vigorous exercise were compared in adults.
- Moderate exercise resulted in the highest maximum plasma F concentration (Cmax).
- Area Under the Curve for plasma F concentration against time was also highest with moderate exercise.
- Moderate exercise may increase the fraction of systemically absorbed F, producing a biological effect.

GRAPHICAL ABSTRACT
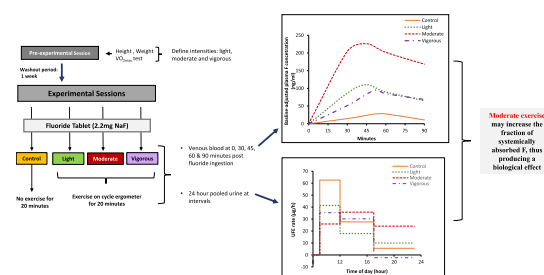
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ABSTRACT

The literature is sparse in terms of the effect of exercise on the pharmacokinetics of fluoride (F) in humans. In a 4-treatment repeated measures cross-over study, we investigated F pharmacokinetics following no exercise (control) and three exercise intensity conditions (light, moderate and vigorous) in healthy adults. At a pre-experimental session, 8 participants (18-30y) residing in a non-fluoridated-area, underwent a $VO_{2 max}$ test to guide the three exercise intensities for the experimental sessions. Participants were on a F-free regime one week before and throughout the four experimental weeks. We measured urinary F excretion (UFE), maximum plasma concentration (Cmax), lag time of Cmax (Tmax), and Area Under the Curve (AUC) for plasma F concentration against time, following F ingestion then no, light, moderate and vigorous exercise. Results showed no statistically significant difference in Tmax among all sessions; whereas Cmax for moderate exercise (226.2 ng/ml) was significantly higher than for no (27.0 ng/ml; $p < 0.001$), light (105.6 ng/ml; $p = 0.016$) and vigorous (94.2 ng/ml; $p = 0.008$) exercise. Mean AUC over 0 −90 min following F ingestion was also significantly higher in moderate exercise than for no ($p < 0.001$), light ($p = 0.004$) and vigorous ($p = 0.001$) exercise. Mean UFE over 0−14h was 638.8, 718.7, 574.6 and 450.5 μg for no, light, moderate and vigorous exercise, with no statistically significant differences among different sessions. In conclusion, this human experimental study suggests that moderate exercise may increase the fraction of F absorbed systemically which is therefore available to produce a biological effect. Future studies should be conducted with larger samples, different age groups and using different F doses.

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1. Introduction

While the effectiveness of topical exposure to fluoride (F) in the prevention of dental caries has been well demonstrated, excessive exposure to systemic F can have some health side effects including dental and skeletal fluorosis (ten Cate and Buzalaf, 2019). Undesirable health effects of F can be related not only to the body's total F intake but, more importantly, to the extent of F retention in the body. Genetic and environmental factors such as stage of skeletal development, acid-base balance and exercise have been suggested to influence metabolism and body retention of F (Buzalaf and Whitford, 2011; Buzalaf, 2018). Understanding F metabolism and its physiological characterisation is therefore very important if we are to avoid or minimise side effects of systemic F exposure.

The pharmacokinetics of F is mainly controlled by pH and storage in bone, because the coefficient of permeability of lipid bilayer membranes to hydrogen fluoride (HF) is a million times higher than to F ion (Buzalaf and Whitford, 2011). Therefore, factors affecting systemic pH (in cells, tissues and fluids) could play an important role in the body's absorption, distribution, excretion and retention of F. After absorption, F concentrations of plasma rise promptly due to the rapid absorption of F from the stomach and reach their peak within 20−60 min. Plasma F concentration normally returns to pre-ingestion levels during the next few hours depending on the F dose. Plasma F concentrations are not homeostatically controlled and therefore fluctuate according to the F dose, body deposition and excretion. Under normal conditions, almost 60% of a healthy adult's and 45% of a healthy child's daily absorbed F is excreted in urine and most (about 99%) of the body-retained F is associated with calcified tissues (Buzalaf and Whitford, 2011).

F has been reported as one of a few known agents that can stimulate osteoblast proliferation (Palmer and Wolfe, 2005). However, different doses of F display a biphasic effect on osteoclast cell viability, differentiation, formation and function: a low F dose stimulates them, whereas a high dose inhibits them (Yu et al., 2018). Furthermore, a decline in expression of osteocytes but a rise in expression of osteoblasts has been linked to exercise (Schwab and Scalapino, 2011), in particular weight-bearing exercise (Willems et al., 2017). Therefore, the pharmacokinetics of F may be influenced by alterations in physiological responses to acute and chronic exercise. Changes in body F retention could be important in terms of the effect of F on tooth and bone development and the timing of F ingestion when fluorides are used in dental caries prevention.

The literature is sparse and contradictory in terms of the effect of exercise on pharmacokinetics of F in humans. The only human experimental study, comparing F concentration in plasma and urine between exercised and non-exercised groups, reported higher plasma F concentrations with moderate and vigorous intensity exercise as well as a reduction in urinary F excretion with moderate exercise compared with a non-exercised control in young adults (Zohoori et al., 2015). Conversely, two animal studies have reported a significant reduction in plasma F concentration in rats exposed to a 1-h treadmill running exercise (Whitford, 1996; Lombarte et al., 2013). More recently, an animal study (Amaral et al., 2018) reported no effect of high intensity training exercise on plasma F in fluorosis-susceptible mice.

The aim of this present study was to investigate the F pharmacokinetics following no exercise and three exercise intensity conditions (light, moderate and vigorous) in healthy adults. The objectives were to compare urinary F excretion (UFE) and plasma F concentration among no, light, moderate and vigorous exercise intensities.

2. Methods

2.1. Participants

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human participants were approved by the Research Governance and Ethics Committee, School of Health and Social Care, Teesside University (Protocol number 066/15). Prior to the experiment, all participants provided written informed consent.

The target sample size for this exploratory study was eight participants, based on the only human study by Zohoori et al. (n = 9) (Zohoori et al., 2015) as well as the animal studies by Whitford (n = 8) (Whitford et al., 1988), Lombarte et al. (n = 10) (Lombarte et al., 2013) and Amaral et al. (n = 8) (Amaral et al., 2018).

The study participants were healthy adult volunteers, from both genders; aged between 18 and 35 years; weighing over 50 kg; with no history of acid-base disturbance and not receiving a therapeutic diet. Participants had to be considered at least moderately active according to the International Physical Activity Questionnaire (i.e. 5 or more days of moderate-intensity activity of at least 30 min per day) (Craig et al., 2003) and "ready" to engage in the prescribed exercise according to the Physical Activity Readiness Questionnaire (American College of Sports Medicine, 2007). All participants were residing in a non-fluoridated area, with a water F concentration of <0.3 ppm.

2.2. Experimental design

This experiment was designed as a four-treatment repeated measures cross-over study, comparing observations within individuals.

2.2.1. Pre-experimental procedures

Participants were invited to attend a pre-experimental session, when height and weight was measured using a stadiometer (Leicester Height Measure, Child Growth Foundation, London, United Kingdom) and a calibrated scale (Seca 220, Seca Weighing and Measuring Systems, Germany). Each individual participant underwent a $VO_{2 \, max}$ test, performed following a standard cycle ergometer protocol (Evans and White, 2009) to determine the exercise intensities (light, moderate and vigorous) for the experimental sessions. Following a 5-min warm up at 25 Watts, the test started at 25 Watts with the intensity being increased by 25 Watts every 2 min until exhaustion. Cycle ergometer power output (PowerTap Cycleops400, USA) and participant's Rate of Perceived Exertion (RPE) using the CR-10 RPE scale (Noble et al., 1983) were recorded every minute. Heart rate was monitored throughout the exercise sessions with a heart rate monitor (Polar RS400, Polar Electro Oy, Finland) and recorded at every minute during exercise. The three exercise intensities (light, moderate and vigorous) were determined by using the v-slope method (Beaver et al., 1986) and defined for each participant as: (i) light intensity: one load below Ventilatory Threshold (VT) 1; (ii) moderate intensity: the load at VT and; (iii) vigorous intensity: one load above VT.

In order to minimise F exposure from all other sources during the study, participants were placed on a F-free regime one week before, as well as during, the whole experimental period. They were provided with a F-free toothpaste to use and instructed to avoid drinking tea, beer and tap-water (if leaving their stated residential area) and eating seafood during the washout and experimental periods (i.e. for a total of five consecutive weeks). Participants were asked to refrain from performing exercise, other than habitual

walking, for 48h prior to and during experimental sessions.

2.2.2. Experimental sessions

After the one-week washout period, each participant underwent four randomly allocated experimental sessions; one no-exercise (control) session and three exercise sessions at different intensities (light, moderate and vigorous) with approximately a week's gap between sessions (Fig. 1).

The study was conducted in an exercise laboratory at the same time of day for all experimental sessions to control for circadian rhythms.

Participants attended the laboratory at around 9:00 a.m. on each experiment day, having fasted overnight. A venous cannula was inserted into the antecubital fossa of each participant's arm, by an experienced nurse, for intravenous blood samples collection (as explained in the next section). A baseline venous blood sample (5 ml) was collected from each participant before they were provided with a low-F breakfast (<10μgF) which comprised a cereal bar, a banana and fruit juice. In order to control the influence of F from diet during the experimental sessions, the same standardised low F breakfast was consumed by all participants at approximately the same time in each of their four sessions.

After breakfast, all participants (in both control and exercise sessions) were given a 1mgF tablet (Endekay Fluotabs 2.2 mg NaF, Manx Pharma Ltd, Warwick, UK) to ingest. Participants then either rested (control session) or undertook the exercise (exercise sessions) at approximately 9:30am. Participants from the exercise group were fitted with a heart rate monitor belt (Polar RS400, Polar Electro Oy, Finland). Participants warmed up for 5 min at a self-selected speed before initiating the designated exercise intensity on the cycle ergometer for 20 min.

2.3. Sample collection

2.3.1. Urine samples

Pooled urine samples were collected by spontaneous voiding over a 24h cycle during four time periods: 1) A nocturnal sample collected from midnight before the experimental (control or exercise) session up until about 09.00am (Baseline, pre-F tablet/pre-exercise); 2) A '09.00am to 12.00pm' sample during the experimental session (0–3h post-F tablet ingestion); 3) A '12.00pm−17.00pm' sample during the experimental session

(3−8h post-F tablet ingestion) and; 4) A '17.00pm through to just before bed-time' sample (~23.00pm) on the experimental day (8−14h post-F tablet ingestion).

2.3.2. Blood plasma

A 5 ml venous blood sample was collected after overnight fasting, prior to taking breakfast (Baseline, T0). An additional four blood samples (5ml/sample) were then collected at 30, 45, 60 and 90 min after ingestion of the F-tablet, providing samples T1 to T4.

2.4. Analytical procedure

F concentration (μg/ml) of urine samples was measured directly after adding total ionic strength adjustment buffer III (Orion Research) to standards and samples, using a F-ion-selective electrode (F-ISE, Model Orion 9609BNWP, Thermo Scientific, USA) coupled to a potentiometer (Model 720A+). F concentrations in plasma (ng/ml) and breakfast items (μg/g) were measured, in triplicate, by a hexamethyldisiloxane (HMDS)-facilitated diffusion method (Taves, 1968) which has been previously reported in detail (Martínez-Mier et al., 2011). In summary, 1 ml H_2SO_4 saturated with HMDS was added to 1 ml of sample (and standards) in a petri-dish and left at room temperature to diffuse overnight. An alkaline solution (50 μl of NaOH (0.05 N), placed as 5 drops on the inside of the dish lid), was used to trap the released F. After a minimum of 16h diffusion, the NaOH drops were combined as a single drop and 20 μl acetic acid (0.20 N) added. The F-ISE electrode was then placed in contact with the combined solution and the mV reading recorded. A calibration curve was used to calculate F concentration of the sample.

The reliability of the methods used was specifically confirmed by re-analysis of a minimum 10% of samples. All sample analysis and re-analysis was conducted in triplicate.

2.5. Data handling and analysis

2.5.1. Urine

Urinary F excretion (UFE) in each individual time-controlled urine sample was calculated by multiplying the F concentration (μg/ml) of the urine sample by its corresponding volume (ml). Baseline-adjusted UFE was calculated by subtracting the baseline UFE from the UFE of each sample. The sums of the amount of F
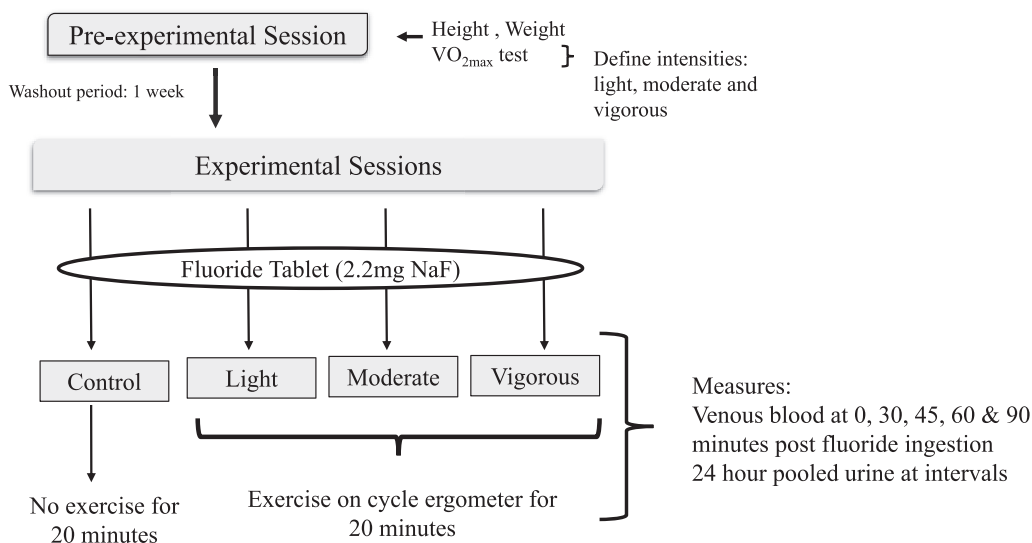

Fig. 1. Experimental procedure and sample collection.

excreted in urine for the periods during and after each experimental session for each participant were used to calculate the total post-F tablet UFE (Periods 2−4 inclusive: representing a 14h period).

The UFE rate (μg/h) for each given time period was calculated by dividing UFE for each time period by the duration of the corresponding collection period (h).

Overall relative UFE (%) was calculated by dividing the baseline-adjusted UFE (μg) for a given time period by the ingested F dose (i.e. 1 mg = 1000 μg) multiplied by 100.

2.5.2. Plasma

Baseline-adjusted plasma F concentration (ngF/ml) was calculated by subtracting the baseline plasma F concentration from the F concentration in each plasma sample.

Maximum F concentration (Cmax) was calculated using the mean maximum baseline-adjusted plasma F concentration following F dose. Lag time to maximum F concentration (Tmax) was estimated using graphs plotting plasma F concentration against time. Area under the curve (AUC) (ng/min/ml) was calculated using the following equation:

$$AUC = \sum_{i=0}^{n-1} 0.5(c_i + c_{i+1})(t_{i+1} - t_i)$$

where:

(t) is the number of minutes after F dose - the first time point is time 0 and (Ci) is the value of C at time t_i.

2.6. Statistical analysis

Descriptive data are presented and statistically significant differences among groups were initially detected using repeated measures ANOVA and further investigated using a post-hoc test (Tukey). Statistical significance was set at $\alpha < 0.05$ and all analysis performed using SPSS version 22.

3. Results

All those invited participated and eight participants (4 males and 4 females) took part in the study. The mean (SD) age, height, weight and BMI for females were: 23.7 (7.2) years, 165.5 (3.5) cm, 64.2 (2.5) kg and 23.5 (1.6) kg/m², and for males were: 25.0 (6.0) years, 176.2 (6.0) cm, 74.2 (9.9) kg and 23.7 (2.1) kg/m², respectively.

3.1. Accuracy of the analytical method

The accuracy of the analytical method was confirmed by comparing the analysis and re-analysis measurements. The results showed no statistically significant differences between the two sets of measurements. The mean (SD) difference for urine samples was 0.009 (0.002) mgF/l (n = 16) and for plasma samples was 0.004 (0.001) ngF/ml (n = 20).

3.2. Comparison of control (no exercise) and the three different exercise intensities

Mean (SD) exercise loads for light, moderate and vigorous exercise intensities were 62.5 (37.5), 87.5 (37.5) and 112.5 (37.5) Watts for females and 68.7 (37.0), 106.2 (37.0) and 137.5 (37.5) Watts for males, respectively. Mean (SD) maximum heart rates (HR) were 176.0 (12.6) and 160.7 (25.7) bpm and mean RPEs (Rate of Perceived Exertion) at the end of the VO₂ max test were 4.7 (0.8) and 7.7 (1.3) in females and males, respectively.

Mean (SD) plasma F concentrations, during the control and exercise sessions, according to the different time periods are presented in Table 1 and the pharmacokinetic variables in Table 2.

Overall, a total of 32 experimental sessions were undertaken by the eight participants. Mean (SD) baseline fasting plasma F concentration was 31.80 (26.2) ng/ml. Mean baseline-adjusted plasma F concentrations across the 90 min post-F ingestion for all experimental sessions are shown in Fig. 2.

All experimental sessions followed a similar trend in plasma F concentration, peaking between 30 and 60 min post-F ingestion with a Tmax ranging from 43 min for light exercise to 50 and 51 min for control and vigorous exercise, respectively. The highest Cmax was found for moderate exercise (226.2 ngF/ml) followed by light (105.6 ngF/ml), vigorous exercise (94.2 ngF/ml) and control (27.0 ngF/ml). AUC(0−90min) ranged from 15058 ngF/min/ml for moderate exercise to 1474 ngF/min/ml for control.

Repeated measures analysis of variation (ANOVA) showed no statistically significant difference in Tmax among all sessions, whereas Cmax for moderate exercise was statistically significantly higher compared to no (p < 0.001), light (p = 0.016) and vigorous (p = 0.008) exercise. AUC(0−90min) was also statistically significant higher at moderate exercise intensity compared to no (p < 0.001), light (p = 0.004) and vigorous (p = 0.001) exercise.

The mean (SD) UFE at baseline was 109.2 (100.7) μgF for the total of 32 experimental sessions undertaken overall by the eight participants. Mean (SD) UFEs for the different time periods during the control and exercise sessions are presented in Table 3.

No statistically significant differences in UFE were found between the no exercise and three different exercise intensities for any individual time period, nor for total post-F tablet period (i.e. 0-14h post-F tablet ingestion).

Mean baseline-adjusted UFE rates across the 4 time-controlled periods of urine collection are shown in Fig. 3.

Light, moderate and vigorous intensity exercise resulted in lower mean baseline-adjusted UFE rates over the 0−3h post-F tablet period (light 41.1, moderate 25.6 and vigorous 35.3μgF/h) in comparison with no exercise (62.6μgF/h); however, the differences were not statistically significant. Furthermore, there were no statistically significant differences in baseline-adjusted UFE rates among different exercise intensities (including no exercise) for any individual time period.

Mean overall relative UFE (i.e. proportion of ingested F dose excreted in urine) for each time period was 21% for 0−3h post-F tablet, 20% for 3−8h post-F tablet and 16% for 8−14h post-F tablet, with an overall relative UFE of 59% for 0−14h post-F tablet.

4. Discussion

This study provides the first data on the effects of exercise on F pharmacokinetics in healthy adults. The results suggest that moderate exercise may result in higher F absorption and consequently higher body F retention. These observations could be particularly important in communities with fluoridation programmes such as school-based milk fluoridation where children consume fluoridated milk just before mid-morning playtime (e.g. in UK school milk fluoridation programmes).

The mean Tmax (50 min) and AUC(0−90min) (1474 ngF/min/ml) reported in our study for the control session (no exercise, received 1mgF tablet) were within the corresponding ranges of 43.1−56.6 min and 752−1562 ngF/min/ml, respectively, reported for 21−35 year old English adults given a F dose of 0.5 mg (500 ml of fluoridated water containing almost 1mgF/L) (Maguire et al., 2005). However, the mean Cmax (27.0 ng/ml) for the no exercise (control) session in our study was higher than the corresponding range of 9.2−19.0 ng/ml reported for English adults (Maguire et al., 2005).

Table 1
Mean (SD) plasma fluoride (F) concentrations (ngF/ml), during experimental sessions; no exercise (control), light, moderate and vigorous exercise.

Post-F ingestion plasma collection time	Exercise intensity			
	No exercise (Control)	Light	Moderate	Vigorous
30 min (T1)	20.4 (14.7)	150.9 (54.9)	241.3 (130.1)	93.8 (36.7)
45 min (T2)	29.6 (16.6)	147.9 (77.5)	263.1 (113.6)	136.9 (59.8)
60 min (T3)	33.6 (26.9)	134.6 (104.7)	238.7 (74.1)	127.5 (24.9)
90 min (T4)	16.6 (12.5)	110.0 (98.7)	205.2 (83.3)	111.4 (42.9)

Table 2
Mean (SD) pharmacokinetic parameters for plasma following ingestion of fluoride (F) tablet (1.0 mg F) by exercise intensity.

Pharmacokinetic parameters for plasma F	Exercise intensity			
	No exercise (Control)	Light	Moderate	Vigorous
T_{max} (min)[a]	50.3 (11.0)	42.9 (13.5)	45.9 (10.5)	51.3 (10.9)
C_{max} (ngF/ml)[b]	27.0 (24.3)	105.6 (41.7)	226.2 (115.6)	94.2 (58.1)
$AUC_{(0-90min)}$ (ngF.min.ml^{-1})[c]	1474 (939)	6920 (3506)	15058 (6596)	5542 (2264)

[a] Lag time to maximum F concentration.
[b] Maximum F concentration.
[c] Area under the curve.
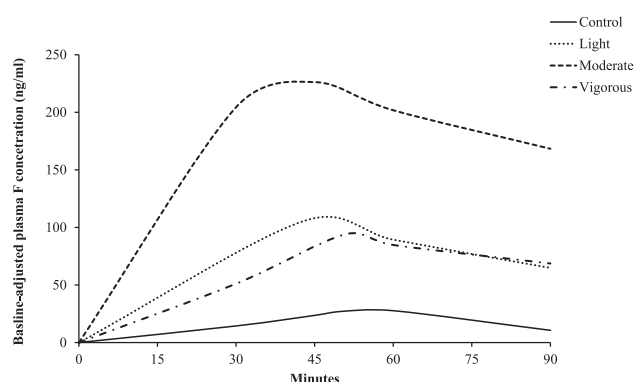
Fig. 2. Baseline-adjusted plasma F concentration (ng/ml) over the 0−90 min post F ingestion period according to exercise intensity.

Since F dose is an important factor influencing F pharmacokinetics, the observed higher pharmacokinetic parameters in our study, compared to the study by Maguire et al. (2005) could be explained by the larger amounts of F ingested by participants in our study.

Our study found a non-statistically significant trend for an overall lower UFE with greater exercise intensity. However, the overall mean plasma F concentrations at different time points, as well as Cmax and $AUC_{(0-90min)}$ were higher for the exercise sessions compared to the no exercise (control) session (Tables 1 and 2; Fig. 1). These findings imply that exercise could affect the pharmacokinetics of F, i.e. increasing F absorption but decreasing F excretion. However, the mechanisms by which exercise could alter F metabolism remain unclear. The increase in cardiac output and consequently muscle and skeletal blood flow following exercise

may lead to an increase in the rate of F absorption and body distribution to muscles and bones. Additionally, exercise could affect renal clearance of F from kidneys in two ways: (a) increase the activity of sympathetic nervous system, resulting in vasoconstriction within the kidney which would then reduce renal blood flow and glomerular filtration rate (GFR); and (b) increase production of lactic acid by muscle which would increase the renal reabsorption of F (Whitford, 1996; Buzalaf and Whitford, 2011). These changes would further lessen the renal excretion of F but tend to increase levels of F in plasma.

Our study found no statistically significant difference in Tmax among different intensities of exercise including no exercise (control). However, our study showed that the mean values for Cmax and $AUC_{(0-90min)}$ were statistically significantly higher for moderate exercise compared with light and vigorous exercise as well when compared with no exercise (control). A study with nine adults (Zohoori et al., 2015) also reported higher plasma F concentrations, although not statistically significant, for moderate intensity exercise compared with control, light and vigorous exercise. Gastric emptying has been shown to increase with increasing exercise intensities up to 65% VO$_2$ max (moderate intensity), but it decreases above an intensity of 75% VO$_2$ max (vigorous intensity) (Neufer, 1989). Cardiac output following an increased work rate increases in an almost linear manner to meet the increasing oxygen demand but only up to the point where maximal capacity is reached (Manley, 1996). This may explain the higher mean plasma F concentration, Cmax and $AUC_{(0-90min)}$ for the moderate compared to vigorous exercise as participants may have reached their maximum cardiac output when exercising at vigorous intensity. Future studies are therefore needed to include interventions where participants undertake an exercise routine at different intensities

Table 3
Mean (SD) urinary fluoride excretion (UFE; μgF) for different time-controlled periods during experimental sessions for no exercise (control), light, moderate and vigorous exercise.

UFE (Time period)	Exercise intensity			
	No exercise (Control)	Light	Moderate	Vigorous
UFE$_{0-3h}$ (9:00−12:00)	302.7 (354.4)	222.3 (64.0)	119.4 (132.4)	213.5 (100.0)
UFE$_{3-8h}$ (12:00−17:00)	214.0 (167.8)	207.4 (116.4)	242.9 (100.3)	130.8 (74.1)
UFE$_{8-14h}$ (17:00−23:00)	130.3 (122.2)	196.0 (206.7)	207.8 (134.7)	124.5 (52.5)
UFE$_{0-14}$ (09:00−23:00)	638.8 (565.5)	718.7 (296.8)	574.6 (281.1)	450.5 (206.1)

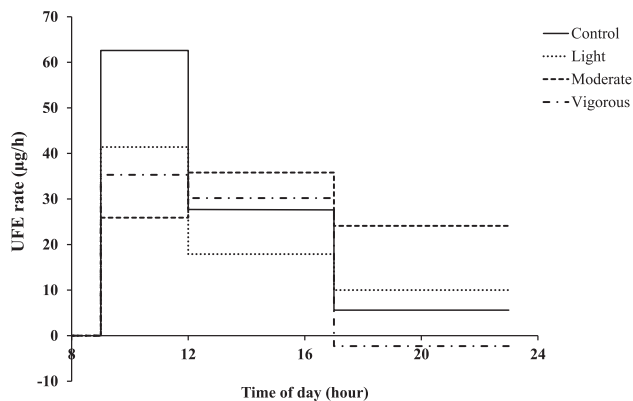**Fig. 3.** Mean baseline-adjusted UFE rate (μgF/h) across the 4 time-controlled periods of collection according to exercise intensity.

(light, moderate and vigorous), for a prolonged period of time.

Urine is the major excretion route for systemically absorbed bioavailable F, with the majority of an ingested F dose appearing in the urine within the first 3 h (Zipkin and Leone, 1957). Our study showed that, on average, 59% of daily intake of F was excreted in urine, over a 24h period, which is in agreement with the suggested corresponding figure of 60% for healthy adults (Buzalaf and Whitford, 2011). Our study also found that, on average, 21% of ingested F dose was excreted in urine during the first 3 h following F ingestion, corresponding to the value of 20% reported for healthy adults (Zipkin and Leone, 1957).

Our study showed a lower, although not statistically significant, UFE rate over the first 3h period for moderate exercise compared with light and vigorous exercise as well as when compared with no exercise (Table 3). However, the UFE rate tended to be higher over the 3−14h period for moderate exercise compared with other exercise intensities including no exercise. These findings indicate that moderate exercise may lead to a delay in urinary F excretion in adults. The lower UFE rate over the first 3h period could be explained by the increased production of lactic acid, leading to a more acidic urine and consequently resulting in a higher proportion of ingested F being reabsorbed (i.e. lower urinary F excretion). In addition, it is known that a steady-state relationship exists between plasma F levels and the hydration shell of the bone crystallites (Rao et al., 1995). Thus, another possibility is that moderate exercise increases the absorption of F, thus augmenting plasma F levels, which in turn would increase F uptake in the hydration shell of the bone crystallites. As plasma F levels start to decrease after the peak is reached, then F present in the hydration shell of the bone crystallites is released back into plasma and excreted in urine over time.

In order to reduce dental caries in children, public health initiatives such as school fluoridated milk programmes have been rolled out across schools in some counties including the UK (Banoczy et al., 2009). However, previous studies have indicated that current UK milk fluoridation programmes do not provide adequate protection for the prevention of dental caries (Ketley and Lennon, 2000). It has been reported that increasing the school milk F dose from 0.5 mg to 0.9 mg per 189 ml, in the UK, may still be too low to achieve the World Health Organisation recommended UFE concomitant with optimal F exposure for children aged < 6y (World Health Organization, 2014). In the UK, fluoridated milk, is often provided to schoolchildren during their mid-morning break before undergoing physical activity. In addition, UK children's physical activity levels during break have been reported to be predominantly moderate (Powell et al., 2016). According to our findings, the low UFE observed (Maguire et al., 2013) during monitoring of fluoridated milk programmes may therefore be related to the effect of moderate physical activity, that children undertake during their breaks, on F absorption and excretion. F concentrations in blood and urine have been shown not to be influenced by sex (Torra et al., 1998; Del Carmen et al., 2016) However, due to the possible different physiological responses following exercise in children compared to adults, as well as females compared to males, further work is required to determine the effects of exercise on F metabolism in young children and different sexes. These findings can help inform the evidence base for stakeholders and decision makers in dental public health as well as health professionals who may wish to review F dose and time of administration in different fluoridation programmes.

The main limitations of our study are: (i) the sample size; although the number of participants in this study are comparable with other similar studies in humans (Zohoori et al., 2015) and animals (Whitford et al., 1988; Lombarte et al., 2013); (ii) the F dose; which was based on the optimal F concentration of drinking water of 1 mg/l, and; (iii) the inclusion of only one age group (young adults). Since the peak plasma and bone F concentrations are directly related to both the age of the individual and F intakes, any extrapolation of the study findings to other age groups should be made with caution.

Our study also indicated large variation in pharmacokinetic variables between individuals. A study by Ekstrand [Ekstrand, 1978] with a family of five, aged 10−38 years old, who ate together and received a water supply with 9.6 ppm F, showed a large variation in plasma F concentration between family members and a much greater within-individual variation during the day (e.g. 40−110 ng/ml for an adult family member). Some of the relatively wide variation in pharmacokinetic variables between participants might be explained by between-individual differences in physiological variables such as volume and pH of gastric secretions, gastro-intestinal motility, plasma volume, and urinary pH.

In conclusion, this human experimental study adds to the understanding of the effects of exercise on F metabolism. The findings suggest that moderate exercise may increase the fraction of ingested F absorbed systemically and therefore available to produce a biological effect. In addition, moderate exercise may have a tendency to delay the excretion of F in urine.

Credit author statement

FV Zohoori: Conceptualization, Methodology, Funding acquisition, Writing − Original draft, Supervision. M Mahmood: Methodology, Investigation, Data curation, Validation, Writing − Original draft. LB Azevedo: Methodology, Writing − review and editing, Supervision. M Buzalaf: Methodology, Writing − review and editing, Supervision. A Maguire: Methodology, Validation, Writing − review and editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

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