The alkalizing supplement referred to as “AlkaPlex” in this study was created using NION Health® technology and was an early iteration of NION granules.

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An Alkalizing Nutrition Supplement That Positively Influences Measures of Health and Aerobic Performance

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ABSTRACT

A previously studied alkalizing nutrition supplement (ANS) was shown to positively influence both anaerobic performance and submaximal exercise capacity, but the influence of this ANS on aerobic performance is less understood. This study tested whether ingestion of the same ANS would influence measures of submaximal and maximal aerobic performance. Twenty-eight participants (16 men, 12 women) performed two incrementally graded treadmill exercise tests to volitional exhaustion using a double-blind, placebo controlled, crossover design. After a 7-day loading phase of either placebo or AlkaPlex®-based ANS tablets (1 tablet/22.7 kg body mass), participants completed a treadmill test that included standardized moderate (MI) and high intensity (HI) submaximal stages for measures of steady-state heart rate (HR), respiratory exchange ratio (RER), blood lactate (BL), and rating of perceived exertion (RPE). The submaximal test at HI was continued to volitional exhaustion with successive 1-min stages to measure maximal HR (HRMAX) and RER (RERMAX), maximal oxygen consumption (VO2MAX), and time-to-exhaustion (TTE). Measures of blood pH, bicarbonate, and base excess were also determined for the same testing time points. Two-factor repeated measures ANOVA were used to detect difference by condition (ANS versus placebo tablets) and time point of the measurement with post-hoc planned contrasts (α=0.05). Measures of HR, BL, and RPE were significantly lower (P=0.02-0.001) for the ANS condition, while RERMAX (+0.06), BLMAX (+1.1 mmol/dl), VO2MAX (+1.44 ml/kg/min), and TTE (+0.6 minutes) were all significantly higher (P=0.02-0.002) for the ANS tablet condition. Lastly, blood pH was higher at rest and post-exercise while bicarbonate was non-significantly higher at all measures for the ANS tablet condition. The 7-day ingestion of ANS tablets had small-moderate positive ergogenic effects on submaximal and maximal treadmill exercise test measures, as well as significantly higher blood pH values. These effects are like those described for use of alkalizing agents (but without side effects) and alkaline-promoting diets.

1. Introduction

Chronic low-grade metabolic acidosis, a condition commonly associated with a Western-style diet, has been associated with increased risk for cardiovascular, kidney, and bone disease, as well as hypertension and all-cause mortality (1-2). While the degree to which these health risks can be altered with chronic changes in diet alone appears to be controversial (1,3,4), short-term (acute) consumption of alkaline diets and alkaline-based nutrition supplements have been shown to significantly improve markers of both health and physical performance (5-9). Limmer et al. (8), for example, recently reported faster 400-m running performance for recreational runners after a 4-day low-PRAL diet (i.e., Potential renal acid load) relative to the same performance attempt after a 4-day high-PRAL diet. The PRAL measure, which is based upon an evaluation of dietary intake records, is a common way to describe the effect of dietary acid load on the body where low- and high-PRAL are referring to diets presumed to be more alkaline and acidic promoting, respectively (10). As such, low-PRAL diets are believed to promote higher circulating bicarbonate in the blood over high-PRAL diets such that improved high intensity physical performances may be expected. In another study, Caciano et al. (5) used short-term (4-9 days) low-PRAL and high-PRAL diet interventions and a crossover design to determine that short-term anaerobic performance, but not aerobic performance (i.e., time to exhaustion from a graded exercise test), was significantly improved following the low-PRAL diet. The results for both studies (5,8) support the idea that short-term alkaline-based dietary interventions (i.e., low PRAL) can impact measures of anaerobic performance when extracellular buffering of excess hydrogen ions via the bicarbonate buffering system is expected to be a performance-limiting factor (11).

Short-term use of alkaline-promoting nutrition agents, such as sodium bicarbonate ($NaHCO_3$) and sodium citrate, have also been shown to improve high intensity exercise performance by enhancing the extracellular bicarbonate buffering system (12). In a previous study, our lab evaluated the influence of an AlkaPlex®-based alkaline nutrition supplement (hereafter referred to as ANS) on cardiorespiratory and blood lactate responses during a constant power double-poling test, as well as maximal upper body power performance in trained cross-country skiers (7). Using a 7-day loading phase and a crossover design that included the use of placebo tablets, the skiers experienced lower cardiorespiratory and blood lactate measures during the submaximal constant power test, as well as higher upper body power measures during maximal power testing, while reporting only minor side effects from ingesting the ANS tablets. These responses are consistent with those expected from acute ingestion of an alkalizing diet or supplement (5,8), but the study results were not complimented with blood measures of pH and bicarbonate to directly link the use of this supplement with an enhanced bicarbonate buffering capacity. In addition, while the ANS clearly improved measures of anaerobic performance in the skiers (7), the effects of this ANS supplement on endurance performance (e.g., maximal oxygen uptake (VO_{2MAX}) or treadmill time-to-exhaustion (TTE)) have yet to be tested.

Interestingly, Caciano et al.'s (5) low-PRAL diet intervention was also associated with small increases in both VO_{2MAX} and TTE over the high-PRAL diet intervention, but both changes were borderline non-significant (P=0.085 and 0.120, respectively). It is likely that this study's relatively small sample size of 10 was simply not powered to detect significant changes in either VO_{2MAX} or TTE. Thus, if we assume that these changes in VO_{2MAX} and TTE are real, and we also assume that low-PRAL diets and ANS supplementation have similar alkaline promoting effects on exercise metabolism, then it seems likely that ANS supplementation may positively influence markers of aerobic performance.

Therefore, the primary purpose of this study was to extend our original evaluation (7) of this AlkaPlex®-based ANS to determine whether supplementation would positively influence markers of aerobic performance. As such, our primary outcome measures included VO_{2MAX} and TTE from an incrementally graded exercise test to volitional exhaustion.

A secondary goal was to broaden the scope of outcomes from our previous study (7) to include measures of both urine pH and specific gravity, blood pH and buffering capacity, as well as evaluate select measures at rest just prior to exercise testing. Both primary and secondary outcome measures were determined to support the hypotheses that a 7-day loading phase of the AlkaPlex®-based ANS tablets would be associated with positive physiological changes at rest (i.e., lower blood pressure, increased blood pH, better hydration status via increased urine specific gravity), during submaximal exercise (i.e., increased blood pH; increased measures of blood bicarbonate and select ions; decreased measures of blood lactate), as well as at maximal intensity aerobic exercise (i.e., increased maximal blood lactate, cardiorespiratory measures, VO_{2MAX}, and treadmill time to exhaustion).

2. Method

2.1. Participants

Recreationally active college-aged adults were recruited from the surrounding area to visit the Movement Science / Human Performance Lab on the Montana State University campus for testing. Participants also needed to be able to commit to the study's timeline which concentrated all testing within 3-4 successive weeks. Prior to any testing, participants read and signed an informed consent document that was approved by the MSU Internal Review Board and were screened for contraindications to high intensity treadmill exercise testing using standard procedures (13).

2.2. Experimental Design

This study was designed as a randomized, double-blind, placebo-controlled, crossover trial (Figure 1). Both the ANS and placebo tablets were provided by the ANS tablet manufacturer to the testing lab within containers labeled only as tablets "A" and "B", respectively, so that neither the subjects nor the investigator knew the identity of the tablets during testing. The identity of the tablets was revealed only after all testing and data analyses were completed. Following the first treadmill test (described below), participants were randomly assigned to either Group A or Group B which corresponded to consuming ANS and placebo tablets, respectively, during the first loading phase I (Figure 1). The only criteria that delimited group assignments was that each group was balanced by gender.

2.3. Procedures

Participants completed three treadmill exercise testing visits (Figure 1). The first lab visit served to habituate the study participants to performing a treadmill test, while the test itself also provided baseline information for standardizing subsequent treadmill testing visits. During the second and third lab visits, each participant performed both submaximal and maximal treadmill testing protocols that followed each 7-day loading phase for either ANS or placebo tablets. As noted in Figure 1, these 7-day loading phases were separated by a 7-day washout phase which allowed both tablets to be naturally cleared from the body before the second loading phase began. After the washout phase, each group was assigned the second tablet (i.e., crossover) for the second 7-day loading phase, after which the second and last set of submaximal and maximal testing protocols occurred. Testing for all participants was completed within a 4-week period.

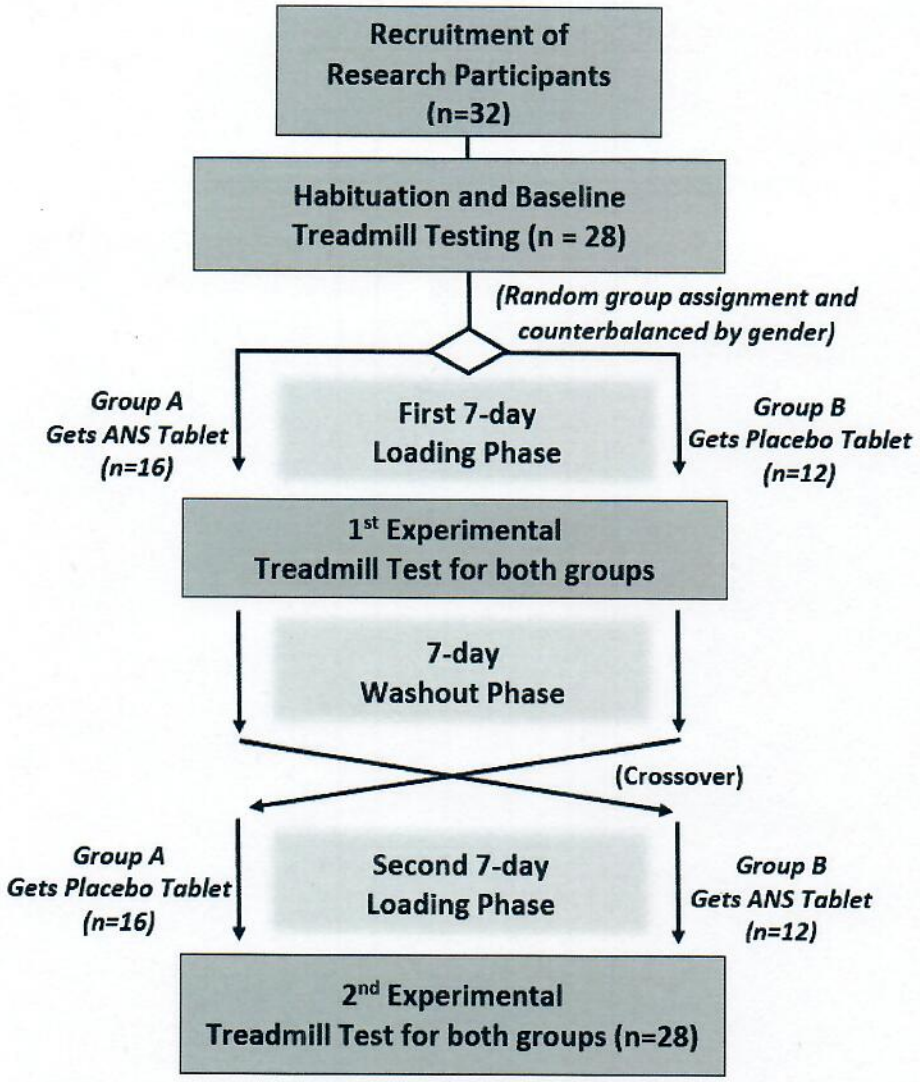

Figure 1. *Schematic representation of experimental design and data collection strategy.*

2.4. Baseline Treadmill Testing

This lab visit served to familiarize each participant with the submaximal treadmill testing procedures, as well as provide a basis for constructing a series of submaximal test stages and maximal protocol to be used during the subsequent experimental treadmill testing. First, participants sat quietly for 5 minutes before having resting blood pressure assessed with a manual sphygmomanometer and stethoscope. Next, after measuring body height and mass to the nearest 0.1 cm and kg (Health-o-Meter beam scale, Continental Scale Corp., Bridgeview, IL), respectively, participants performed a self-paced warm-up on a motorized treadmill for 10 minutes which included ≥1 minute at a self-perceived high intensity. Participants were then setup with measurement equipment that included a chest strap for telemetry-based heart rate monitoring, as well as a face mask and a small backpack-mounted device for measuring oxygen uptake (VO_2). The treadmill test was structured as a series discontinuous walking or running stages where each participant could choose to

either walk or jog, but all three treadmill tests had to be the same exercise modality so that physiological measures between tests could be compared. Each walking or running stage was discontinuous and included four minutes of exercise at a fixed speed and grade, and then one min of slow walking at the same grade, for a total of five minutes at each stage. While the 4-min exercise bout was used to establish a submaximal steady-state, the 1-min slow walking between stages was needed for fingertip blood sampling for both blood lactate and blood pH. Each participant completed between four and seven of these 5-min stages with each stage increasing the intensity of exercise until the participant was observed to have reached or exceeded their lactate threshold (LT), which was defined as: 1) Having a lactate of ≥4.0 mmol/dL for the last 4-min stage, and 2) having a change in blood lactate of ≥1.0 mmol/dL between the last two successive stages. Near the end of each 4-min stage, participants were asked to assess their Rating of Perceived Exertion (RPE) using the 1-10 category-ratio scale (14). Once LT was observed, the participant was transitioned immediately into an active warm down on the treadmill for another five minutes. From each baseline treadmill test, a 3-5 stage submaximal protocol was created for use during the next two experimental treadmill tests. The highest two stages were designed to correspond to moderate intensity ($3 \leq RPE < 5$) and high intensity ($5 \leq RPE < 7$) where the high intensity stage was also at or slightly above measured LT. As such, the moderate and high intensity submaximal stages served as comparative standards (i.e., everyone was at similar relative exercise intensity) for the experimental treadmill tests.

2.5. First 7-Day Loading Phase

At the end of the baseline treadmill lab testing visit, participants were given their tablets to consume over the next seven days (i.e., first 7-day loading phase) at the same dosage prescribed by the manufacturer – i.e., Dose was proportional to baseline testing body mass (1 tablet/22.7 kg = 1 table/50 lbs). If a participant's body mass was equivalent ≥10% of a whole tablet, then the dosage was rounded up to the next whole tablet dose – e.g., a dose equivalent to 2.5 tablets for a 57 kg body mass would have been rounded up to 3 tablets. The dosage for the first loading phase was recorded and replicated exactly for the second loading phase regardless of any subsequent changes in body mass. The exact morning and evening tablet dosage was proscribed to each participant using a 7-day pill container (Ezydose™ Weekly / AM-PM Pill Planner; Apothecary Products, Burnsville, MN USA) with the daily dosage split between morning (before 11:00 AM) and evening (after 5:00 PM) times. To document any possible side effects of consuming either ANS or placebo tablets, participants were given a 7-day paper-based gastrointestinal (GI) distress and symptom checklist that would be completed only if there were GI symptoms to report that may have related to the consumption of the tablets. The format of this symptom checklist was based upon a similar checklist reported by Cameron et al. (15) for a study involving the consumption of $NaHCO_3$.

Participants were also instructed to return to the lab one morning during the loading phase (i.e., on day 3, 4, or 5 of loading phase) to provide a midstream first morning urine sample collected and transported within a urine specimen cup. This urine sample, which was preferably collected within 60 minutes of lab arrival, was immediately evaluated for pH and specific gravity (SG) with an automated desktop analyzer (Accustrip URS Reader; Jant Pharmacal Corporation, Encino, CA USA) and test strips (Accustrip URS 10 reagent test strips; Jant Pharmacal Corporation, Encino, CA USA). Each sample was measured in duplicate with results for urine pH and SG averaged across analyses. If duplicate SG analyses were not within 1% of each other, a third analysis was completed and the results for the two samples within 1% of each other were then used for averaging. The urine pH data were used as an indirect indicator whole-body shifts in acid-base status where consumption of the ANS tablets would be expected to cause urine pH to become more alkaline (higher pH) (16). The urine SG data, in turn, were used as an indirect indicator of whole-body hydration status where

lower urine SG is interpreted as a being more hydrated than higher urine SG (17). During this same visit, participants also received a 237 ml (8 oz) nutrition shake (Ensure Original Nutrition Shake; Abbott Laboratories, Chicago, IL USA) to consume 2-4 hrs prior to their next scheduled treadmill test. The purpose of the nutrition shake was to provide the same light standardized meal (220 kcals that included 33 g carbohydrate, 9 g protein, and 6 g fat) to all participants prior to each experimental treadmill test.

2.6. Experimental Treadmill Test Visit

Since the first and second experimental treadmill tests were administered identically to each other, only a single description of this testing is given within this section. On the 7th day of the loading phase, each participant returned to the lab to perform the standardized submaximal stages described previously, as well as complete a maximal treadmill test to volitional exhaustion to collect measures of blood lactate, maximal oxygen consumption (VO_{2MAX}), and time to exhaustion (TTE). Prior to arriving at the lab, participants were instructed to avoid consuming caffeinated beverages/food, as well as to consume nothing but the nutrition shake (except water ad libitum) within 2-3 hrs of arriving at the lab. In addition, participants were also instructed to avoid any high intensity exercise the day before treadmill testing, as well as any exercise on the day of testing prior to arrival. Once in the lab, the participants provided another urine sample (collected within 60 minutes of arrival and analyzed as described above) and were immediately reassessed for body mass and height before sitting for five minutes quietly. Next, a pre-testing fingertip blood sample was collected and then resting blood pressure assessed. Next, after participants warmed-up for 10 minutes on the treadmill, they were readied for the start of the treadmill test (i.e., chest strap for heart rate monitoring and the mask and backpack for measuring VO_2). Note that the modality of testing – i.e., walking or jogging – was the same as that chosen by each participant during the baseline treadmill testing. Each test began with the 3-5 stages determined from the baseline treadmill test with each stage lasting five minutes and included a 4-min bout of submaximal exercise that was followed 1-min bout of slow walking where fingertip blood samples were collected for both blood lactate and blood pH. Once the submaximal stages were completed (i.e., the standardized high intensity stage was always the last submaximal 5-min stage), the treadmill stages changed to 1-min each with treadmill speed and/or grade progressively increasing the exercise intensity each minute until volitional exhaustion – i.e., the participant could not maintain the exercise intensity despite verbal encouragement. Once the test ended, the participant performed a walking cool down for another 10 minutes while an immediate post-test fingertip blood sample was collected to determine maximal blood lactate (BL_{MAX}, mmol/dL). The highest 20-sec sample averaged VO_2 value was considered to be VO_{2MAX} if ≥3 of the following criteria were satisfied: 1) A leveling of VO_2 values as evidenced by ≤2.0 ml/kg/min change between last two stages; 2) A maximal heart rate (HR_{MAX}, BPM) within ±10 BPM of age-predicted HR_{MAX} (i.e., 220-Age); 3) A maximal respiratory exchange ratio (RER_{MAX}) ≥1.10 before the test ended; 4) A maximal RPE (RPE_{MAX}) of 9 or 10. The variables derived from successfully completing the maximal portion of this test included VO_{2MAX}, HR_{MAX}, RER_{MAX}, RPE_{MAX}, BL_{MAX}, as well as time-to-exhaustion (TTE, mins), the latter of which was the total time between the end of the last submaximal stage and the end of the maximal test (i.e., time spent within the 1-min stages).

2.7. 7-Day Washout and Second 7-Day Loading Phase

After completing the first experimental treadmill test, each participant completed a 7-day "washout" period where neither group consumed tablets. Since the contents of both tablets were known to be water soluble and not stored by the body, the 7-day period was considered sufficient. Participants visited the lab once on days 6 or 7 of the washout too

provide another urine sample (as described previously), as well as collect their tablets for the beginning of the second phase. After completing the washout, both groups began the second 7-day loading phase with the other tablet – i.e., The crossover where Group A was now consuming placebo tablets and Group B was now consuming ANS tablets (Figure 1). The tablet dosages were prescribed identically to that of the first loading phase while also using the same tablet dispensers and GI symptom checklists. Note that the pill dispensers were washed between loading phases to avoid any possible cross contamination of the two types of tablets. Lastly, participants also visited the lab to provide another morning urine sample and collect a nutrition shake for the last treadmill test.

2.8. Walking Versus Running Testing Protocols

Given the recreational backgrounds of the research participants, this study allowed the participants to choose either walking or running submaximal and maximal treadmill testing protocols. Similar to the protocol described by Kline et al. (18), the walking protocol had participants choose a "brisk" walking speed on a level grade near the end of their warm-up during baseline treadmill testing. The treadmill speed corresponding to this self-selected "brisk" pace was then fixed for both submaximal and maximal testing with stages differing by changes in grade (i.e., +2.5% per stage) until volitional exhaustion. The running protocol, in contrast, required participants to provide an estimate for current 5 km running time which, in turn, was converted into an average 5 km race pace. While at a level grade, the first three running stages corresponded to running speeds of approximately 65%, 75%, and 85% of 5 km race pace with stages thereafter increasing by +2.0% grade each stage and no change in treadmill speed until volitional exhaustion.

2.9. ANS Nutrition Supplement

The ANS tablets used for this study, which are the same as those described previously (7), are considered a mineral supplement with each tablet containing a crystalline composition called AlkaPlex® (1000 mg) that includes calcium (245 mg), magnesium (2 mg), and potassium (35 mg). According to the ANS manufacturer (pH Science Holdings, Inc., Lynnwood, WA USA), the ANS ingredients are allowed by both the U.S. and World anti-doping agencies (i.e., WADA), while AlkaPlex® was granted New Dietary Ingredient (NDI) recognition by the U.S. Food and Drug Administration (FDA). In addition, according to independent testing of the ANS tablets that was contracted by the ANS manufacturer, the ANS tablets have a pH of 12.75 (Note: For a comparative reference, the pH of sodium bicarbonate is 8.35). The placebo tablets, which were formulated and provided by the ANS manufacturer, had a similar size, color, shape, and texture as the ANS tablets while lacking the AlkaPlex® active ingredient. The ANS and placebo tablet dosing quantity (1 tablet/22.7 kg body mass/day), frequency (split over morning and evening), and duration (7-day ingestion period), were also identical to that described previously (7). Minor side effects for participants consuming both placebo and ANS tablets (e.g., minor GI disturbances; unusual color of urine and feces) have been reported (7), but none of those effects were enough to alter either participants' usual dietary and exercise habits, or their participation in the study. Regardless, the subjects in the current study were instructed to track any side effects during both loading phases as described above.

2.10. Instrumentation

Open-Circuit Indirect Calorimetry

Standard indirect open-circuit calorimetry procedures with a portable metabolic measurement system (Oxycon Mobile, Viasys Healthcare, Yorba Linda, CA) were used to record submaximal and maximal measures of VO_2, HR, and RER. This system was mounted to a modified hydration backpack (Slipstream; Camelbak Products, LLC; Petaluma, CA)

which was worn by each participant during treadmill testing. The oxygen and carbon dioxide analyzers were calibrated prior to each test using a certified gas mixture. Both analyzers, as well as the ventilation meter, were calibrated prior to each test according to the manufacturer's guidelines. While the metabolic system collected breath-by-breath data, these data were then reported at either 60-sec sample intervals (i.e., submaximal treadmill testing) or 20-sec sample intervals (maximal treadmill testing) for all subsequent analyses. Lastly, measures of HR were recorded by the metabolic system using the telemetry signal from a Polar Accurex Plus heart rate monitor chest strap and transmitter (Polar Electro, Inc., Lake Success, NY).

Blood Lactate Analyzer

The handheld Lactate Pro analyzer (Arkray, Inc., Kyoto, Japan) was used to measure whole blood lactate from a single fingertip blood droplet during treadmill testing. A detailed description of our lab's use of this monitor has been described previously (7) while others (19) have described the monitor's accuracy and reliability. For the current study, blood lactate was evaluated at each submaximal treadmill stage for each of the three treadmill test visits, as well as for determining BL_{MAX} at the end of the maximal protocols.

i-STAT Blood Analyzer

In addition to the blood lactate analysis, additional fingertip capillary whole blood droplets were collected within 100 µl capillary tubes. This blood was then transferred to a disposable CG8+ cartridge (Abbott Point of Care Inc., Princeton, NJ USA) and then analyzed for a collection of chemistries and electrolytes, hematology, and blood gas measures with the i-STAT analyzer (Abbott Point of Care Inc., Princeton, NJ USA). The i-STAT is a handheld point-of-care device developed originally for bedside medical applications but has since been used in settings where quick evaluations are needed, such as hospital intensive care units (20) or sports science labs (15). When compared to a conventional laboratory blood gas analyzer, Sediame et al. (21) reported that the i-STAT provided very comparable blood gas analyses. For the current study, the i-STAT was used to analyze blood samples collected at four time points for each of the experimental treadmill test visits: 1) At rest (before the warm-up and testing began); 2) During the 5th minute of the standardized moderate intensity submaximal testing stage; 3) During the 5th minute of the standardized high intensity submaximal testing stage; 4) Within one minute of completing the maximal treadmill test (during recovery). From each of these analyses, a selection of electrolytes (Na^+, K^+, Ca^{2+}) and blood gas measures (blood pH, base excess, HCO_3) were recorded for later analysis. The reason for including the electrolytes within this analysis is that two of these – i.e., K^+ and Ca^{2+} - are components of the ANS tablets.

2.11. Statistical Analyses

Summary measures for cardiorespiratory (SBP, DBP, HR, VO_2, RER), blood lactate (BL), RPE, TTE, blood electrolytes (Na^+, K^+, Ca^{2+}), blood gases (blood pH, base excess, HCO_3), as well as urine pH and specific gravity (SG), were summarized at several points (as described earlier) for the treadmill tests that corresponded to the consumption of each type of tablet. Each of these variables were then statistically evaluated using a 2-factor repeated measures ANOVA (Tablet Type x Time Point) (α=0.05). In addition, the effect size (ES) for each comparison of interest was calculated using Cohen's d (22): $ES = (V_{ANS} - V_{Placbo})/(\text{Pooled SD})$, where V_{ANS} and V_{Placbo} were the sample mean values corresponding to the ANS and placebo conditions, and SD_{Diff} was the standard deviation of these differences. Common practice guidelines were then used to interpret the magnitude of ES values for this study – i.e., $0.2 \leq$ "small" ES < 0.5, $0.5 \leq$ "medium" ES $<$

0.8, and "large" ES ≥ 0.8. Finally, a minimum sample size of 27 was needed to detect a minimum 0.5 effect size (i.e., about 30 secs for TTE) at a 0.05 alpha and power of 0.80 for measures of aerobic performance (G*Power Version 3.0.10; Universität Kiel, Germany) (23).

3. Results

Summary descriptive characteristics for the 28 participants who completed all testing visits are provided in Table 1. While body mass was measured for all treadmill testing visits, Table 1 reports only that for the first experimental treadmill test (Figure 1) since the values did not differ statistically with those from the second experimental treadmill test (73.9 kg versus 73.8 kg; P=0.38). Additionally, both resting systolic (Mean±SD (ES): 120±12 vs 125±10 mmHg (small ES of *-0.45*); P=0.01) and diastolic blood pressures (78±5 versus 82±7 mmHg (medium ES of *-0.67*); P=0.001) were significantly lower when measured at rest and at the end of the ANS loading phase.

Table 1. *Summary of descriptive characteristics for study participants (Mean ± SD (range)).*

Group	Age (years)	Body Height (cm)	Body Mass (kg)	BMI (kg/m^2)
Women (n = 12)	21 ± 4 (18-33)	165.4 ± 7.0 (153.7-178.3)	65.1 ± 2.8 (56.5-79.1)	24.4 ± 2.4 (19.8-28.2)
Men (n = 16)	19 ± 2 (18-26)	179.7 ± 6.2 (166.9-189.5)	70.8 ± 2.4 (56.5-79.1)	24.7 ± 3.2 (19.3-30.8)
Total Sample (n = 28)	20 ± 3	173.6 ± 9.7	68.3 ± 3.8	24.5 ± 2.8

NOTE: BMI = body mass index = [(body mass, kg)/ (body height, $m)^2$]

Prior to the planned ANOVA analyses, the data were analyzed for both gender and treatment order effects. Neither of these variables were significant so the ANOVA analyses were performed as described previously. Table 2 highlights several significant differences in cardiorespiratory and blood lactate measures between tablet conditions from the experimental treadmill tests. Submaximal HR at the moderate (MI) stage, for example, was significantly lower for the ANS condition (P=0.03), while HR_{MAX} was non-significantly higher for the ANS condition (P=0.12). Measures of RER for both MI and HI stages were statistically similar (P=0.58-0.60; very small ES values), but RER_{MAX} was significantly higher for the ANS condition (P=0.002; medium ES). Interestingly, both RPE (P=0.02-0.006; small ES) and blood lactate (P=0.02; small ES) for MI and HI stages were significantly lower for the ANS condition with BL_{MAX} being significantly higher for the ANS condition (P=0.001; small ES). In addition, measures of both relative VO_{2MAX} (49.14±8.73 versus 47.70±9.16; P=0.002: very small ES of *+0.16*) and absolute $VO2_{MAX}$ (3.6±0.9 vs 3.5±0.8 L/min; P=0.002; very small ES of +0.12), as well as TTE (4.6±1.1 versus 4.0±1.2 mins; P=0.001; medium ES of *+0.52*) were all significantly higher for the ANS condition.

Table 2. *Summary of heart rate (HR), the respiratory exchange ratio (RER), rating of perceived exertion (RPE), and blood lactate (BL) collected during both moderate intensity (MI) and high intensity (HI) steady-state exercise, as well as those values associated with either maximal aerobic exercise intensity (HR, RER, RPE) or immediate post-exercise (BL). All values (n=28) expressed as Mean ± SD along with the effect size (ES) for each paired comparison.*

Variable	Tablets	MI Aerobic Exercise	HI Aerobic Exercise	Maximal Aerobic Exercise
HR (BPM)	**Placebo**	169 ± 13	183 ± 9	197 ± 6
	ANS	†166 ± 11	181 ± 8	199 ± 6
		(-0.25)	*(-0.24)*	*(+0.33)*
RER	**Placebo**	0.99 ± 0.06	1.06 ± 0.05	1.34 ± 0.12
	ANS	1.00 ± 0.07	1.05 ± 0.06	†1.40 ± 0.11
		(+0.15)	*(-0.18)*	*(+0.61)*
Rating of Perceived Exertion (RPE)	**Placebo**	3.8 ± 1.2	6.1 ± 1.5	9.6 ± 0.7
	ANS	†3.4 ± 1.3	†5.6 ± 1.6	9.5 ± 0.7
		(-0.32)	*(-0.32)*	*(-0.14)*
Blood Lactate (mmol/dL)	**Placebo**	2.7 ± 0.7	4.4 ± 1.0	11.1 ± 2.7
	ANS	†2.4 ± 0.7	†4.1 ± 0.9	†12.2 ± 2.7
		(-0.43)	*(-0.32)*	*(+0.41)*

† Mean values for ANS condition differed significantly from the placebo condition (P<0.05).

Table 3 summarizes select blood measures reported from the handheld i-STAT device. First, there were no significant differences found for any of these measures between ANS and placebo conditions, though there were several trends worth mentioning. Specifically, blood pH tended to be higher (more alkaline) for the ANS condition at every measure with the highest values being at rest and the lowest being immediate-post maximal exercise. A mean resting blood pH of 7.44 for the ANS condition, in fact, was higher than all other mean values (large ES value of +1.35) except for resting blood pH for the placebo condition. Blood HCO_3 levels were also slightly higher at rest and at moderate intensity exercise, though not significantly, while HCO_3 levels were significantly higher for the high intensity treadmill stage (P=0.008). There were no differences in BE, or for HCO_3 immediate post-recovery, between tablet conditions. Lastly, there were no differences between tablet conditions for any blood ion measures (i.e., Na^+, K^+, Ca^{2+}).

Figure 2 shows changes in both urine pH and SG for urine collected at five separate time points: Both loading phases and experimental treadmill testing days, as well as during the washout phase. Mean Urine pH values of 6.0-6.1 occurred for both placebo tablet conditions (i.e., loading phase and treadmill test), as well as the washout phase, but this value increased non-significantly to 6.4 during the ANS loading phase (medium ES of +0.57) and then significantly to 6.9 on the ANS tablet treadmill testing day (large ES of +1.20; P<0.001). Similarly, urine SG was stabile for most test measures at 1.014-1.016 until the day of the ANS treadmill test where SG decreased significantly to 1.011 (large ES of -0.85; P=0.006). Finally, there was not a single report of negative side effects by participants that could be attributed to consuming either ANS or placebo tablets.

Table 3. Summary of blood pH, bicarbonate (HCO_3), base excess (BE), sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}) collected during rest (pre-treadmill testing), both moderate intensity (MI) and high intensity (HI) steady-state exercise, as well as immediate post (IP) maximal exercise. All values (n=28) expressed as Mean ± SD along with the effect size (ES) for each paired comparison.

Variable	Tablets	At Rest	MI Aerobic Exercise	HI Aerobic Exercise	Maximal Aerobic Exercise
Blood pH	**Placebo** **ANS**	7.41 ± 0.03 †7.44 ± 0.02 *(+1.35)*	7.38 ± 0.03 7.40 ± 0.03 *(+0.66)*	7.36 ± 0.04 7.37 ± 0.02 *(+0.33)*	†7.18 ± 0.08 †7.21 ± 0.07 *(+0.40)*
HCO_3	**Placebo** **ANS**	22.5 ± 1.4 23.1 ± 1.7 *(+0.39)*	21.4 ± 1.8 22.0 ± 1.5 *(+0.36)*	‡19.6 ± 1.8 ‡19.8 ± 1.7 *(+0.11)*	‡12.5 ± 2.3 ‡12.8 ±2.0 *(+0.14)*
BE	**Placebo** **ANS**	-1.9 ± 1.5 -1.9 ± 1.6 *(0)*	-3.6 ± 2.1 -3.2 ± 1.7 *(-0.21)*	‡-5.5 ± 2.2 ‡-5.5 ± 2.0 *(0)*	‡-15.7 ± 3.3 ‡-15.2 ± 3.1 *(-0.16)*
Na+	**Placebo** **ANS**	‡142.4 ± 1.7 ‡142.4 ± 1.5 *(0)*	142.8 ± 1.3 142.8 ±1.6 *(0)*	143.0 ± 1.2 142.8 ± 1.2 *(-0.17)*	144.7 ± 1.8 144.6 ± 1.9 *(-0.05)*
K+	**Placebo** **ANS**	4.8 ± 0.8 4.6 ± 0.4 *(-0.33)*	5.2 ± 0.7 5.2 ± 0.6 *(0)*	5.1 ± 0.3 5.1 ± 0.6 *(0)*	5.3 ± 0.5 5.5 ± 0.5 *(+0.40)*
Ca2+	**Placebo** **ANS**	1.18 ± 0.10 1.19 ± 0.10 *(+0.10)*	1.16 ± 0.06 1.15 ± 0.05 *(-0.18)*	1.16 ± 0.06 1.13 ± 0.05 *(-0.54)*	1.20 ± 0.07 1.16 ± 0.06 *(-0.61)*

NOTE: Placebo and ANS (alkaline nutrition supplement) refer to the types of tablets consumed during the respective 7-day loading phases of the study.

† Mean blood pH value differed significantly from all other mean blood pH values ($P<0.05$).

‡ Mean values for that measurement condition differ significantly from all other measurement conditions ($P<0.05$).

4. Discussion and Conclusions

This study found that ingestion of an AlkaPlex®-based alkaline nutrition supplement (ANS) influenced measures of health and aerobic performance at rest (lower systolic and diastolic blood pressure; better hydration status via a lower urine SG), during submaximal steady-state exercise (lower HR, RPE, and BL responses), as well as during maximal aerobic exercise (increased RER_{MAX}, BL_{MAX}, VO_{2MAX}, and TTE). In fact, the changes in both VO_{2MAX} and TTE support the premise that ANS supplementation positively influenced markers of aerobic performance as hypothesized. In addition, measures of blood pH and bicarbonate levels were higher at every measurement time point for the ANS tablet condition, though none of these differences were statistically significant despite a moderate effect size (Table 3). Further, there were no side effects reported by the participants for ingestion of either the ANS or placebo tablets. Lastly, these results compliment those from a previous study that found the same ANS tablets to be associated with lower steady-state cardiorespiratory and blood lactate measures, as well as higher levels of maximal anaerobic performance (7). Collectively, these results support the hypothesis that a 7-day loading phase of the ANS tablets provided a mild (i.e., mostly low-moderate effect sizes) ergogenic effect for both submaximal and maximal outcome measures as derived from a common treadmill test of aerobic performance.

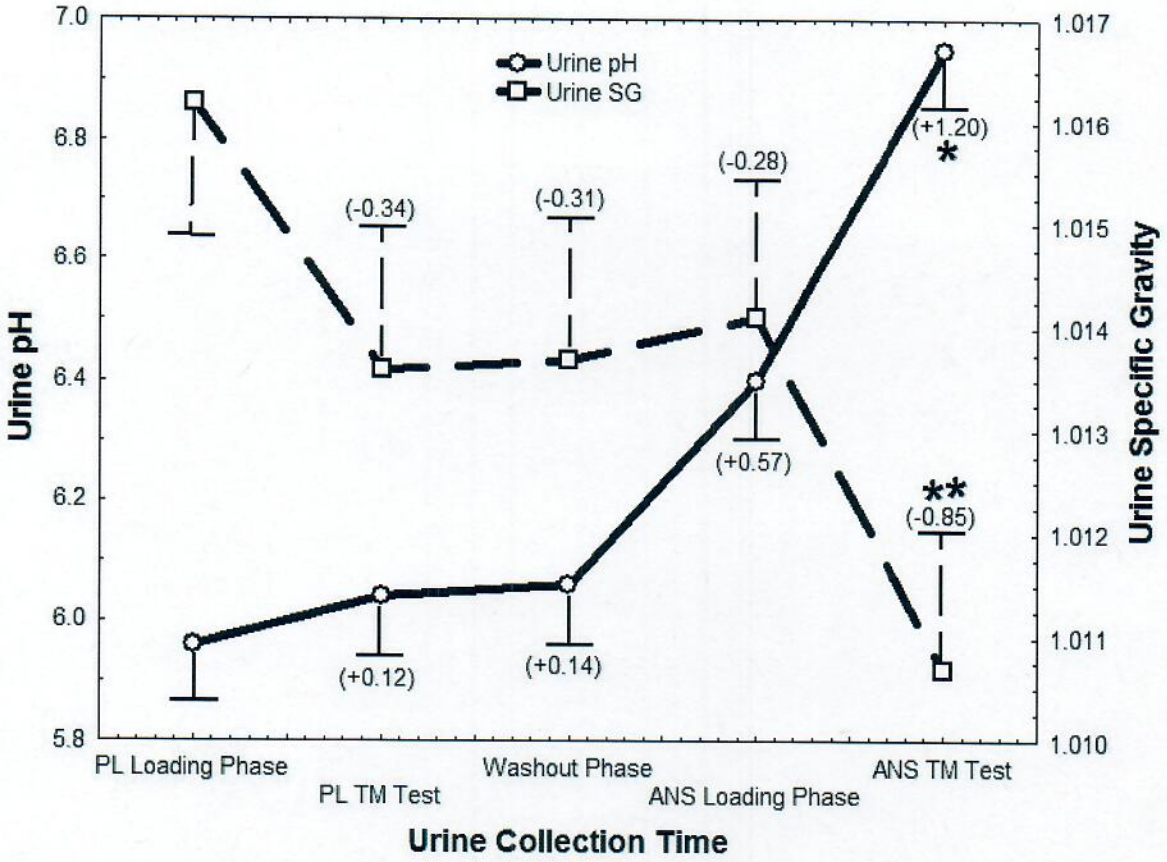

Figure 2. *Measures of urine pH and specific gravity (SG) at five different collection time points: The end of the placebo loading phase; The day of the placebo experimental treadmill test; The end of the washout phase; End of the ANS loading phase; The day of the ANS experimental treadmill test. All values (n=28) expressed as group means with one-sided SE bars. Effect size reported for each value relative to that for measures during the placebo loading phase reported in parentheses. NOTE: * Mean urine pH was significantly higher than that for all other measurement times (P<0.001); ** Mean urine SG was significantly lower than that for the placebo loading phase (P=0.006).*

4.1. Maximal Outcome Measures

A primary goal of the present study was to test whether ingestion of the ANS tablets could improve measures of aerobic performance – i.e., VO_{2MAX} and/or TTE from the maximal treadmill test. In fact, measures of both VO_{2MAX} (+1.44 ml/kg/min and +0.1 L/min for relative and absolute VO_{2MAX}, respectively) and TTE (+36 secs) improved significantly along with RER_{MAX} (+0.06), but these results appear to both support and conflict with results in the published literature. Niekamp et al. (9), for example, observed that subjects with a low-PRAL diet (i.e., alkaline promoting) had a significantly higher RER_{MAX} (+0.06) from a treadmill test to exhaustion than those consuming a high-PRAL diet (i.e., acidic promoting). If short-term ANS ingestion in the current study promotes a similar systemic alkaline state as a low-PRAL diet, then the identical increase in RER_{MAX} of +0.06 between these studies was expected (Table 2). The same research team (5) later reported nonsignificant increases in both absolute VO_{2MAX} and TTE from an incrementally graded exercise

test to exhaustion. In fact, their reported increases in VO_{2MAX} (+0.15 L/min) and TTE (+1.05 minutes) were greater than that for the current study (+0.10 L/min and +0.50 minutes, respectively). The difference in significance between these reports is probably anchored to the outcome measures on which each study was powered and the subsequent sample size determinations. Caciano et al. (5), for example, was powered to detect small differences in RER_{MAX} which gave a minimal sample size of 10 (actual sample size = 10), whereas the current study was powered to detect small differences in TTE which required a sample size of at 27 (actual sample size = 28). The choice to power on TTE by the current study, therefore, created the need for a much greater sample size which, in turn, provided more statistical power to detect differences within other outcome measures of interest, such as VO_{2MAX}. Thus, if it is assumed that Caciano et al. (5) was simply underpowered to detect differences in either VO_{2MAX} or TTE (which seems to be the case), then their results are consistent with those from the present study rather than contradictory.

In addition to TTE, the current study reports a statistical increase in both absolute (+0.10 L/min) and relative (+1.44 ml/kg/min) VO_{2MAX} for the ANS tablet condition, but these differences also had very small effect sizes (ES<0.20). In fact, these differences equate to 2.8-3.0% of the overall mean VO_{2MAX}, which is considerably less than the 5.6% reported for day-to-day variation in VO_{2MAX} in healthy adults (24). Thus, even though VO_{2MAX} was statistically higher for the ANS tablet condition, this difference was not practically significant because it does not exceed that expected by daily variation alone. If this is true, then why do both Caciano et al. (5) and the present study report higher values of TTE and VO_{2MAX} for treadmill tests to exhaustion following alkaline-based nutrition interventions? First, it is well known that metabolic acidosis is a primary contributor to muscular fatigue during high intensity exercise (25,26). It is also well established that use of nutritional agents (e.g., $NaHCO_3$ and sodium citrate) can induce a pre-exercise metabolic alkalosis that functions to delay muscular fatigue and improve physical performance by enhancing the extracellular buffering capacity (25,26). Further, if ingestion of both low-PRAL diets and the ANS tablets help resist the influence of exercise-induced metabolic acidosis in this same manner (5,7-9), then it stands to reason that the inevitable onset of volitional exhaustion at the end of a maximal treadmill test could be delayed – i.e., an increased TTE. In the current study, a delayed onset of fatigue for the ANS tablet condition was evidenced by a significantly higher BL_{MAX} (12.2 versus 11.1 mmol/dL; Table 2) which suggests the working muscles were able to perform more work, or work at a higher intensity, just prior to the onset of volitional exhaustion. Lastly, since many non-athletically trained adults can satisfy the criteria for achieving VO_{2MAX} without a concomitant plateau in VO_2 (i.e., a peak VO_2 instead of true VO_{2MAX}) (27), then the increased TTE is what could have allowed the measured VO_{2MAX} to be closer to that VO_2 plateau. In short, we believe that the effect of ingesting the ANS tablets was to increase TTE by delaying the onset of muscular fatigue which, in turn, allowed participants to achieve a rate of VO_2 that was closer to their true VO_{2MAX}.

Given that previous research with these ANS tablets (7), low-PRAL diets (5,8), and traditional alkalizing agents (e.g., $NaHCO_3$) (25) have all been shown to improve anaerobic performance, it is possible that this study's increase in TTE with the ANS tablets were more related to improved anaerobic capacity as well. The ability to exercise, for instance, within the exercise intensity range that spans between the onset of lactate threshold and the measurement of VO_{2MAX} is a function of metabolic energy generation from both aerobic and anaerobic pathways (28). As aerobic exercise intensity approaches that which elicits VO_{2MAX}, measures of VO_2 will classically begin to plateau which indicates a maximal rate of aerobic energy generation has been reached. Continuing to exercise at even higher intensities is possible if the rate of anaerobic energy generation has not yet been slowed by metabolic acidosis. Thus, if the ingestion of the ANS tablets enhanced extracellular buffering capacity as proposed, then the effect on maximal treadmill testing would be to enhance anaerobic energy generation after aerobic energy metabolism had reached its maximal rate (i.e., VO_{2MAX}). Thus, enhanced

extracellular buffering capacity will function to improve anaerobic energy generation and high intensity work performance, and this is true whether the performance is truly an anaerobic task – i.e., 400 m sprinting (8) – or a task that requires high energy generation from both aerobic and anaerobic energy systems – i.e., the very end of a maximal treadmill test to exhaustion. In both instances, enhanced physical performance is dependent upon the extracellular bicarbonate buffering system to minimize the effects of metabolic acidosis and resist the onset of fatigue.

4.2. Standardized Submaximal Testing

During the standardized moderate (MI) and high intensity (MI) treadmill stages, steady-state measures of HR, blood lactate, and RPE were all slightly, though significantly, lower for the ANS tablet condition at one (MI only for HR) or both stages (HR, BL, RPE). We reported lower values of HR and BL previously after a 7-day loading phase with the same ANS tablets for well-trained cross-country skiers doing a simulated double-poling activity (7). Taken together, these results indicate lower cardiovascular stress and a perception of less effort during standardized work output tasks. In addition, submaximal RER values for both ANS and placebo tablets in this study statistically similar (Table 2) which is the same as that reported by Niekamp et al. (9) when comparing the influence of low- and high-PRAL diets. Collectively, these data support the premise that extracellular alkalization, whether it be by use of a low-PRAL diet or ANS tablet ingestion, can improve markers of submaximal exercise capacity.

4.3. Hydration Status and Resting Blood Pressure

This study found that both hydration status (i.e., lower urine SG) and resting blood pressure (SBP and DBP) improved when measured at the end of the 7-day ANS tablet loading phase. While it is well known that extreme changes in hydration status and blood pressure can be linked, whether the improved hydration status in this study, in fact, caused a lowering in both SBP and DBP cannot be determined. The improved hydration status, however, was expected because a previous study reported improved hydration status following regular consumption of a mineralized bottled water that contained a dissolved low-dose version of the same AlkaPlex®-based ANS used by this study (6). Several studies have also shown that acidic diets (i.e., high-PRAL) have been positively associated with higher SBP and DBP (1). Thus, if the consumption of these ANS tablets has an equivalent influence to that of consuming a low-PRAL (alkalizing) diet, then the mechanism of influence on blood pressure is more likely related to controlling the influences of metabolic acidosis rather than hydration status.

4.4. Blood pH and Bicarbonate

Sodium bicarbonate (0.3 g/kg body mass) has been shown to acutely increase blood pH and bicarbonate within 60 minutes of ingestion while at rest (7.39 to 7.47, and 24.03 to 30.33 mmol/L, respectively), and then immediately following a bout of repeated sprints (7.19 to 7.25, and 12.35 to 14.87 mmol/L, respectively) (15). The present study also found that blood pH was significantly higher at rest (+0.03 and large ES) and immediately following the maximal treadmill test (+0.03 and small ES) for the ANS tablet condition (Table 3), though these changes are considerably smaller than that reported by Cameron et al. (15) (+0.06 to +0.08). In addition, blood bicarbonate was non-significantly higher after consuming the ANS tablets (+0.02 to +0.06; Table 3), and these changes were again much smaller than that reported by Cameron et al. (15) (+2.52 to +6.30 mmol/L). Also, from Table 3, base excess did not differ between conditions at any measurement time point which would be expected with non-significant changes in blood bicarbonate. Finally, while the current study did not have a single side effect to report, Cameron et al. (15) suggested that the high incidence of GI

disturbances (e.g., belching, stomach bloating, nausea, stomach cramps, diarrhea, vomiting) reported by their participants may have negatively influenced their subsequent sprint performance abilities. Thus, even though the effects of ANS ingestion in this study on blood pH and bicarbonate were relatively small in comparison to a Cameron's standard pre-exercise dose of $NaHCO_3$, the current study reported improved TTE with no side effects while Cameron et al. (15) reported a host of serious side effects and no effect on performance.

This above discussion highlights the important interaction between digestibility of buffering agents (e.g., $NaHCO_3$) and supplements (e.g., ANS) with any type of side effects. This study used the manufacturer's recommendation for dosing of ANS tablets and that appears to have been a reasonable balanced between having no effects while still providing a measurable, though small, ergogenic effect on performance.

4.5. Study Design Considerations

Study design issues to consider in the future are those related to ANS dose and timing of ingestion. For example, this study chose to replicate the ANS dosing strategy used previously (7), which is the same as that recommended by the ANS manufacturer, but it is not known whether any other dose (higher or lower) would have resulted in the same results. In addition, while the study participants were given specific instructions about tablet consumption, it is not known whether a different timing strategy – especially on the day of treadmill testing – would have caused different results. It is reasonable to suggest, for example, that the same dose (1 tablet/22.7 kg body mass/day) over fewer days (e.g., 1-3 days) could have provided similar effects, or that a higher dose (1.5-2.0 tablets/22.7 kg body mass/day) within a single day could have provided similar effects. In fact, since the ingredients for the ANS supplement are entirely water soluble, it is even possible that day-of-testing tablet ingestion is all that is needed for an observable effect. As has been shown with other extracellular buffering agents (29), both dose and timing of ingestion are critical to understanding how an ANS will influence an individual, as well as how to better predict the onset of side effects. Thus, while the current and past research (7) with these ANS tablets have established that a 7-day loading phase can have both cardiorespiratory, metabolic, and performance effects, no other dosing or timing strategies have ever been investigated. Lastly, except for the pre-treadmill testing nutrition shakes, this study did not control the habitual diets of the study participants. Given that dietary PRAL has been linked directly with the same types of cardiorespiratory, metabolic, and performance effects as the ANS tablets from this study (5,8,9), the lack of dietary control (or at least dietary monitoring for posteriori determination of PRAL) should be considered a possible confounder when testing any alkalizing nutrition supplement.

5. Conclusions

In summary, this study found that after seven days of consuming an AlkaPlex®-based alkaline nutrition supplement, recreationally active college-aged participants were shown to have lower blood pressure and better hydration status at rest, lower cardiorespiratory measures during submaximal exercise, as well as significantly higher measures of maximal aerobic performance (both time-to-exhaustion and VO_{2MAX}). Further, these changes were complimented with higher blood pH values at rest and immediate post-exercise, as well as non-significantly higher blood bicarbonate levels. These results compliment a previous study with the same alkaline nutrition supplement that reported improved cardiorespiratory responses during submaximal exercise and improved anaerobic performance (7). In conclusion, this alkaline-based supplement appears to provide a mild ergogenic effect (i.e., mostly low-moderate effect sizes) that positively effects several markers of aerobic performance and was associated with little or no side effects.

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