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Cold Drinks, Exercise, and Multiple Sclerosis

Chaseling GK, Fillingeri D, Barnett M, Hoang P, Davis SL, Jay O. Cold water ingestion improves exercise tolerance of heat-sensitive people with MS. *Med Sci Sports Exerc.* 2018;50(4):643–48.

Multiple sclerosis (MS) is a progressive neurodegenerative disease of the central and peripheral nervous systems resulting in disruption of nerve conduction due to damage of the myelin sheath. A total of 2.5 million people are currently living with MS worldwide (400,000 in the United States and 19,000 in Australia), making it one of the most common causes of neurologic disability (1,2). Females are more commonly diagnosed with MS as compared to males (2). There are 3 primary clinical phases associated with the progression of MS: preclinical, relapsing-remitting, and secondary-progressive. Clinical disability is typically associated with later stages of the relapsing-remitting phase.

Heat intolerance is a major complication associated with MS and is commonly experienced in hot environments and during bouts of physical activity. In relation to MS, heat intolerance manifests as sudden and debilitating fatigue, which can impact daily functions and reduce quality of life. As a result, persons with MS are frequently advised to remain indoors during hot weather and to limit physical activity to avoid heat-related fatigue (3). To date, several body-cooling strategies have been investigated to mitigate heat intolerance in persons with MS. Although effective in lowering core temperature, strategies such as cold water immersion are often impractical during a person's daily routine or work schedule. Cold water ingestion is currently a recommendation of the National MS Society to lower core temperature during activities of daily living and to mitigate heat intolerance for persons with MS (4).

There is limited research on the effect of cold water ingestion on heat intolerance in MS during physical activity and exercise. It is possible that cold water ingestion can act as a simple, yet effective method in lowering core temperature through internal conduction of the body. The authors of this study state that it is the first to investigate the effects of cold water ingestion on reducing heat intolerance in persons with MS during exercise.

MANUSCRIPT REVIEW

The aim of the study was to compare the effect of cold versus thermal-neutral water ingestion on exercise tolerance in

persons with relapsing-remitting MS in a controlled environment. The authors hypothesized that persons with MS would have improved exercise duration with cold (1.5°C/34.7°F) versus thermo-neutral (37°C/98.6°F) water ingestion when compared to those without MS at a sustained exercise intensity (~40% $\text{VO}_{2\text{MAX}}$) in an environmentally controlled laboratory (30°C/86°F; 30% humidity).

A total of 20 men and women, residing in Sydney, Australia, participated in this study, with 10 participants (4 male, 6 female) diagnosed with relapsing-intermittent MS and 10 age-and-sex matched healthy participants (5 male, 5 female). Inclusion criteria for MS participants were (1) classified as a range of 2.0 to 4.5 (range 0 to 10) on an expanded disability status scale (mild to significant impairment; Figure 1) (5) and (2) self-reported heat intolerance. Inclusion criteria for the control participants were (1) not diagnosed with MS and (2) of similar aerobic fitness ($\text{VO}_{2\text{MAX}}$) to the MS participants. Exclusion criteria were not listed.

This 2-group, counterbalanced, repeated-measures study took place over 3 separate laboratory sessions. Both groups reported to the first session (preliminary trial) to complete a graded submaximal aerobic test on a semirecumbent cycle. The protocol began at 45 W and progressed in 20-W increments per 3-minute stage for a total of 4 stages. During the aerobic test heart rate (HR), oxygen uptake (VO_2), and cycle workload were collected in a 20°C (68°F) laboratory. Following the aerobic test, the Young Men's Christian Association (YMCA) calculation was used to estimate $\text{VO}_{2\text{MAX}}$. Estimated $\text{VO}_{2\text{MAX}}$ was then multiplied by 40% to determine a constant exercise workload (i.e. 40% of $\text{VO}_{2\text{MAX}}$) for sessions 2 and 3.

During sessions 2 and 3 (experimental sessions), all participants were provided cold and thermo-neutral water ingestion with the order randomized. There was a minimum of 48

Score	Status	Walking Ability
10	death due to MS	chair or bedbound
9-9.5	completely dependent	chair or bedbound
8-8.5	confined to bed/chair	chair or bedbound
7-7.5	confined to wheelchair	with aid ≤ 5 yards
6-6.5	walking assistance is needed	with aid ≥ 22-110 yards
5-5.5	increasing limitation in ability to walk	without aid ≥ 110-220 yards
4-4.5	moderate disability	without aid ≥ 350-550 yards
3-3.5	mild-moderate disability	fully ambulatory
2-2.5	minimal disability	fully ambulatory
1-1.5	no disability	fully ambulatory
0	normal neuro exam	fully ambulatory

FIGURE 1. Expanded Disability Status Scale (5).

hours between sessions. Each participant was asked to perform cycling in a climate-controlled chamber of 30°C (86°F) with 30% humidity at 40% $\text{VO}_{2\text{MAX}}$ until volitional fatigue or 60 minutes had elapsed. All participants drank a 3.2 mL·kg⁻¹ of water (thermo-neutral or cold) at exercise minutes 15, 30, and 45. The entire volume of water was consumed in less than 1 minute. Water temperatures were regulated with a thermos and hydrostatic water bath for the cold and thermo-neutral water treatments, respectively. Water temperatures were checked with a standard thermometer 1 minute prior to administration to ensure temperatures ($\pm 0.1^\circ\text{C}$). Several measures were collected for body temperature and HR during the experimental sessions. Rectal temperature was measured using a pediatric thermometer (self-administered to 12 cm past the anal sphincter); skin temperature was measured using skin thermometers at 4 locations on the right side of the body [averaged as mean skin temperature in accordance with previous research (6)]; and HR was measured via 6 lead wireless electrocardiograph.

All 20 participants completed the study without complications, although the MS group had significantly ($P = 0.002$) shorter exercise time as compared to the control group. There was a significant interaction between group and water temperature ($P < 0.001$). The entire control group was able to complete the full 60-minute exercise session for both the thermo-neutral and cold water treatments (sessions 2 and 3). Only 30% of the MS group completed the full 60 minutes of exercise for thermo-neutral session. For the cold water session, 50% of the MS group completed the 60-minute session, and each of the 7 individuals who could not complete the thermo-neutral session exercised significantly longer when ingesting the cold water. There was no significant difference between groups for HR at the 30-minute mark of the constant workload session ($\sim 40\% \text{VO}_{2\text{MAX}}$), regardless of water treatment.

Despite longer exercise durations in the MS group when cold water was ingested, there were no significant

differences in rectal temperature, mean skin temperature, and HR when compared to thermo-neutral water ingestion. Similarly, there were not significant differences detected in rectal temperature, mean skin temperature, and HR in the control group when comparing both exercise sessions.

CLINICAL IMPLICATIONS

Heat intolerance can result in disruption of daily activities for persons with MS and contribute to a reduced quality of life. Not all cooling strategies (i.e. body submersion) are feasible for most individuals amid their daily routines. Simple cooling strategies such as cold water ingestion can have a positive clinical impact on managing heat intolerance throughout the day and during physical activity and exercise for persons with MS. The clinical exercise physiologist might consider the administration of cold water for persons with MS when prescribing exercise and ensure that cold water is available for ingestion.

Although exercise duration was extended by $\sim 30\%$ in the MS group when cold water was ingested, there were no changes in rectal or skin temperatures. The author attributes this finding to the stimulation of cold-afferent receptors located in the oral cavity and on the skin. Similar to research investigating prevention of heat sensitivity in athletes (7), it is possible that stimulation of oral cold-afferent receptors could improve heat tolerance without a reduction of core temperature. Further research examining this neurologic response is required for a better understanding.

The findings of this study only apply to 60 minutes of semirecumbent cycling at a constant workload intensity with cold water ingestion occurring every 15 minutes. Future work may focus on different types of exercise and intervals of water ingestion. Additionally, subjective measures were not assessed and have resulted in this insight not being available. A detailed measure of MS disability (i.e. disease duration and severity) also was not included, is a limitation of the study, and reduces its generalizability.

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Exercise, Inflammatory Parameters, and Obesity

De Souza DC, Matos VAF, dos Santos VOA, Medeiros IF, Marinho CSR, Nascimento PRP, Dorneles GP, Peres A, Muller CH, Krause M, Costa EC, Fayh APT. Effects of high-intensity interval and moderate-intensity continuous exercise on inflammatory, leptin, IgA, and lipid peroxidation responses in obese males. *Front Phys.* 2018;9:567.

According to the World Health Organization (WHO), there are an estimated 502 million adults over the age of 20 years who are obese (1). Obesity is known to result in a low-grade chronic inflammatory response (1). This may be a reason for the relationship of obesity and the development of cardiometabolic disease (1). Adipose tissue has been shown to impact endocrine function associated with regulation of the immune system and inflammation through secretions of pro-inflammatory adipokines (leptin, interferon- γ [INF- γ], tumor necrosis factor- α [TNF- α], and interleukin-4 and 6 [IL-4/6]) (2).

In brief, leptin is associated with the activation of pro-inflammatory phenotype T helper lymphocytes (Th1). T helper lymphocytes are responsible for the immune response to bacterial and viral infections. As a result, Th1 function causes a greater production of INF- γ and TNF- α , which both increase systemic inflammation. To regulate the function of Th1, anti-inflammatory T helper lymphocytes (Th2) will produce IL-4 that is responsible for immune response to allergen agents. The INF/IL-4 ratio can be used to measure the Th1 and Th2 immune function of a human. When this ratio is unbalanced, there will be greater systemic inflammation and often the presence of chronic infection (i.e. respiratory or gastrointestinal infections). In the case of obesity, excess body fat results in greater secretion of pro-inflammatory adipokines and impaired immune function, allowing opportunistic infections to occur and increased risk of cardiometabolic disease (3). When obesity is present, there is greater secretion of leptin and lower secretion of TNF- α , as compared to lean individuals, resulting in an imbalance of the INF/IL-4 ratio and higher systemic inflammation (3).

Moderate intensity exercise in accordance with the American College of Sports Medicine (ACSM) recommendations (4) has been shown to improve inflammation and the immune system responses of sedentary people with obesity (5). A major barrier to exercise adherence is lack of time, which may be improved with shorter duration, higher intensity exercise, such as high-intensity-interval training (HIIT). Some findings suggest that HIIT training may also reduce inflammation in both lean and overweight individuals, similar to moderate intensity exercise (5). Interleukin-6 has been

shown to increase postexercise, where it will have an anti-inflammatory effect by increasing production of IL-4 and potentially restoring the INF/IL-4 ratio in persons with obesity. It is possible that a dose-response relationship between exercise intensity and IL-6 production exists after exercise. On the contrary, it is also purported that HIIT-based training may suppress the immune response, thus reducing secretion of immunoglobulin A (IgA), which is an antibody that plays a role in the immune function of mucus membranes associated with the respiratory system and gastrointestinal tract. Lower IgA is associated with greater risk of infection. The exact effects of HIIT training on inflammation and immune response in sedentary and obese individuals is unknown and could provide clinical insight to exercise programming for this population.

MANUSCRIPT REVIEW

The aim of this randomized crossover study was to compare the acute effects of HIIT versus moderate intensity exercise on the inflammatory response (leptin, INF- γ , TNF- α , IL-4, IL-6, and INF/IL-4 ratio), IgA, and lipid peroxidation (measure of inflammation) in obese males. The criteria used to determine clinical obesity were (1) body-mass index (BMI) $> 30 \text{ m} \cdot \text{kg}^{-2}$ and (2) body composition $> 25\%$. A total of 10 male participants (age = 24.5 ± 2.7 years) living in Brazil were recruited for this study. Inclusion criteria were (1) clinically obese, (2) nonsmokers, (3) sedentary (confirmed via international physical activity questionnaire [IPAQ]), and (4) self-reported weight stability for the last 6 months.

All study participants reported to the laboratory for 4 visits. The first visit included resting measures (i.e. blood pressure and heart rate [HR]), anthropometric measures (i.e. height, weight, BMI calculation, dual x-ray absorptiometry [DXA]), and a graded exercise test on a treadmill. The graded exercise test protocol started at a treadmill speed of $3.0 \text{ km} \cdot \text{hr}^{-1}$ ($1.86 \text{ miles} \cdot \text{hr}^{-1}$) and increased by $1.0 \text{ km} \cdot \text{hr}^{-1}$ ($0.62 \text{ miles} \cdot \text{hr}^{-1}$) each minute until maximal treadmill velocity and HR were achieved. Test termination included the following criteria: (1) $\text{HR} \geq 100\%$, (2) rating of perceived exercise > 18 on the 6–20 scale, or (3) participant requested to stop. For visits 2–4, participants were randomly assigned to 1 of 3 conditions (moderate intensity continuous exercise, HIIT, or control [seated rest]) with 7 days between each session. Moderate intensity exercise was at 60% HR reserve (HRR) for 20 minutes; HIIT was prescribed as ten 1:1 minute intervals (20 minute duration) of 90 and 30% maximal treadmill velocity, respectively; and the control treatment included 25 minutes of sitting. During exercise, HR was continuously recorded and rating of perceived exertion (RPE) was assessed each minute of exercise. Finger-based

blood samples were taken immediately after exercise to analyze lactate levels.

All participants were instructed to report to the laboratory after 12 hours of fasting and were provided a consistent meal with an energy equivalency of 4.5 kcal·kg⁻¹ of body weight diluted in 400 mL of water. Blood samples were taken from the antecubital vein at the following intervals: (1) fasting state, (2) 45 minutes postmeal/pre-exercise, (3) immediately after exercise/sitting, and (4) 60 minutes after exercise. Saliva was collected to measure IgA (1) pre-exercise, (2) immediately after exercise/sitting, and (3) 60 minutes after exercise. Concentrations of leptin, INF- γ , TNF- α , IL-4, and IL-6 for each blood sample was determined via the enzyme-linked immunosorbent assay (ELISA) test. The ELISA test was also used for saliva samples to determine IgA concentrations. The thiobarbituric acid reactive substance (TBARS) test was used as an index of peroxidation of lipids.

As expected, a HIIT training bout resulted in significantly higher HR, RPE, and lactate compared to a moderate intensity continuous exercise bout, confirming the difference in intensity levels. High-intensity-interval training resulted in significantly lower leptin levels immediately after exercise and improved IFN/IL-4 ratio up to 60 minutes postexercise. Moderate intensity exercise resulted in significantly higher IFN- γ , both immediately after exercise and 60 minutes postexercise. Both HIIT and moderate intensity exercise increased IL-6 levels immediately after exercise and 60 minutes postexercise. There were no significant differences in IgA or lipid peroxidation after HIIT and moderate intensity exercise.

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CLINICAL IMPLICATIONS

According to the authors, this is the first study to report changes in the INF/IL-4 ratio in obese-sedentary males. The findings of this study demonstrate that acute bouts of HIIT in sedentary obese men may result in improved immune function immediately after and up to 1 hour postexercise without compromising the mucosal immune response or causing oxidative stress. These findings support the notion that HIIT may have anti-inflammatory benefits for persons with obesity who are beginning exercise both in and out of the rehabilitative setting. This study also indicates that moderate intensity exercise may also improve the immune response by improving the TNF/IL-4 ratio immediately after and 60 minutes postexercise. Results of this study provide additional support for the clinical exercise physiologist to consider incorporating HIIT as an option for obese male clients, when deemed appropriate.

There are several limitations to this study. The authors do not address why the study excluded female participants and a control group for this study. Furthermore, the study only applies to persons with obesity who are young adults (~25 years of age) and does not take into consideration the full range of the adult population or older adults. The findings of this study are specific to acute effects of exercise at very specific workloads and cannot be applied to chronic exercise stimuli or different types of exercise (i.e. resistance training). Future research is required with a more diverse population of participants under multiple exercise stimuli for a more complete understanding of immune and inflammatory responses to exercise in obese individuals.

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