THE EFFECT OF GLYCEMIC INDEX ON INTERLUKIN- 6 CONCENTRATION IN RESPONSE TO ENDURANCE AND RESISTANCE EXERCISE

A DISSERTATION

BY

SAREH HASANI

Presented in Partial Fulfillment of the Requirement for the

Doctor of Philosophy Degree in Exercise Physiology

at Srinakharinwirot University

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AN ABSTRACT

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Sareh Hasani. (2015). *The effect of glycemic index on interleukin- 6 concentration in response to endurance and resistance exercise*. Dissertation, Ph.D. (Exercise Physiology). Bangkok: Graduate School, Srinakharinwirot University. Advisor Committee: Asst. Prof. Dr. Supaporn Silalertdetkul, Dr. Witid Mitranun.

This study examined the effect of glycemic index on interleukin 6 concentration in response to endurance and resistance exercise. Study 1: 10 men completed 1 hour running at 70%-75% VO2max on treadmill on three occasions; high GI and low GI or placebo was consumed by the subjects 45 minutes before exercise. Blood samples were collected before, after, 1hour and 24hours after exercise. Concentration of Plasma IL-6 in LGI group was less than HGI and placebo groups, IL-6 increased significantly after exercise in groups (all $P < 0.05$), also there was significant difference for plasma IL-6 concentration between placebo and low glycemic groups in after exercise (P=.003) and 1hour after exercise (P=.005) . CK was significantly elevated at all- time points after exercise in 3 groups (all $P < 0.05$). Concentration of serum CK in LGI group was less than HGI and placebo groups but there not significantly. The consumption of the LGI beverage before exercise could minimize the increasing of plasma IL-6 concentration immediately after exercise and during the 1 hour recovery period compared with the HGI beverage and placebo. Study 2: 10 healthy males completed 5 sets of 10 lengthening (eccentric) contractions at 120% 1 repetition-maximum. Subjects were randomized to consume the GI beverage (high-GI, low-GI (15% weight per volume; 3 g/kg BM) or placebo in three times within 10 minutes following exercise, and again at 50 and 110 minutes during recovery time. Blood samples (10 mL) were collected before exercise and after 0, 1 hour, 3hours and 24 hours of recovery. Concentration of plasma IL-6 in HGI group was less than LGI and placebo groups. IL-6 increased significantly after exercise in recovery time in 3 groups (all $P < 0.05$), furthermore there was significant difference for IL-6 between placebo and high glycemic groups in 3hours after exercise (P=.016). Concentration of serum CK in HGI group was less than LGI and placebo groups, CK was significantly elevated at all times points during recovery in 3 groups (all $P < 0.05$), except for 1 hour after exercise in HGI group ($P = 0.31$), but there was no significant difference for CK between groups. We concluded that the LGI beverage as pre-exercise meal could modify the inflammatory response in prolonged exercise, and also for resistance exercise HGI carbohydrate during recovery from exercise attenuate plasma IL-6 concentration.

ผลของดัชนีน้ำตาลต่อความเข้มข้นอินเตอร์ลิวคิน-6ในการตอบสนองต่อการออกกำลังกายแบบความทนทานและแรงต้าน

บทคัดย่อ

ของ

สาเร ฮาซานี

เสนอต่อบัณฑิตวิทยาลัย มหาวิทยาลัยศรีนครินทรวิโรฒ เพื่อเป็นส่วนหนึ่งของการศึกษา
ตามหลักสูตรปริญญาปรัชญาดุษฎีบัณฑิต สาขาวิทยาศาสตร์การกีฬาและสุขภาพ
กรกฎาคม 2558

สาเร ฮาซานี. (2558). *ผลของดัชนีน้ำตาลต่อความเข้มข้นอินเตอร์ลิวคิน-6 ในการตอบสนองต่อการออกกำลังกายแบบความทนทานและแรงต้าน*. ปริญญานิพนธ์ ปร.ด. (วิทยาศาสตร์การกีฬาและสุขภาพ). กรุงเทพฯ: บัณฑิตวิทยาลัย มหาวิทยาลัยศรีนครินทรวิโรฒ. อาจารย์ที่ปรึกษาปริญญานิพนธ์: ผู้ช่วยศาสตราจารย์ ดร.สุภาภรณ์ ศิลาเลิศเดชกุล, อาจารย์ ดร.วิทิต มิตรานันท์

การศึกษาผลของดัชนีน้ำตาลต่อความเข้มข้นของอินเตอร์ลิวคิน-6 ในการตอบสนองต่อการออกกำลังกายแบบความทนทานและแรงต้าน การทดลองที่ 1: อาสาสมัครชายจำนวน 10 คน วิ่งด้วยความหนัก 70%-75% VO2max บนลู่วิ่ง เป็นระยะเวลา 1 ชั่วโมง ในสามช่วงการการทดลอง อาสาสมัครบริโภคดัชนีน้ำตาลสูง ดัชนีน้ำตาลต่ำ และสารหลอก ก่อนการออกกำลังกาย เก็บตัวอย่างเลือด ก่อน หลัง 1 ชั่วโมง และ 24 ชั่วโมงภายหลังออกกำลังกาย ความเข้มข้นของพลาสมาอินเตอร์ลิวคิน-6 ในกลุ่มดัชนีน้ำตาลต่ำมีค่าน้อยกว่ากลุ่มดัชนีน้ำตาลสูงและกลุ่มสารหลอก อินเตอร์ลิวคิน-6 เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิตภายหลังการออกกำลังกายในทุกกลุ่ม (ทั้งหมดP < 0.05) นอกจากนี้ยังพบว่าความแตกต่างอย่างมีนัยสำคัญของอินเตอร์ลิวคิน-6 ในพลาสมาระหว่างกลุ่มสารหลอกและกลุ่มดัชนีน้ำตาลต่ำภายหลังการออกกำลังกาย (P=.003) และ 1 ชั่วโมงภายหลังการออกกำลังกาย (P=.005) ครีเอทีนไคเนสเพิ่มขึ้นอย่างมีนัยสำคัญในทุกช่วงเวลาภายหลังการออกกำลังกายในทั้งสามกลุ่ม (ทั้งหมด P < 0.05) ความเข้มข้นของซีรัมครีเอทีนไคเนสในกลุ่มดัชนีน้ำตาลต่ำมีค่าน้อยกว่ากลุ่มดัชนีน้ำตาลสูงและสารหลอกแต่ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ การบริโภคเครื่องดื่มที่มีดัชนีน้ำตาลต่ำก่อนการออกกำลังกายส่งผลทำให้ลดการเพิ่มขึ้นของความเข้มอินเตอร์ลิวคิน-6ในพลาสมา ภายหลังการออกกำลังกายทันที และ 1 ชั่วโมงในช่วงฟื้นสภาพเมื่อเปรียบเทียบกับเครื่องดื่มที่มีดัชนีน้ำตาลสูงและสารหลอก การทดลองที่ 2: อาสาสมัครชายจำนวน 10 คน ทำการยกน้ำหนักจำนวน 5 เซตของ 10 ครั้งของการหดตัวของกล้ามเนื้อแบบยืดยาวออก ที่ 120% ของ แรงหดตัวสูงสุด อาสาสมัครดื่มเครื่องดื่มที่มีดัชนีน้ำตาล (ดัชนีน้ำตาลสูง ดัชนีน้ำตาลต่ำ (15% น้ำหนักต่อปริมาตร ; 3 กรัม/กิโลกรัม น้ำหนักตัว) หรือสารหลอก จำนวน 3 ครั้งภายในเวลา 10 นาที ตามด้วยการออกกำลังกาย และ อีกครั้ง ที่ 50 และ 110 นาทีในช่วงฟื้นสภาพ เก็บตัวอย่างเลือด (10 มม) ก่อนออกกำลังกาย และหลัง 0 1 ชั่วโมง 3 ชั่วโมง และ 24 ชั่วโมงในช่วงฟื้นสภาพ ความเข้มข้นของ อินเตอร์ลิวคิน-6ในกลุ่มดัชนีน้ำตาลสูงมีค่าน้อยกว่ากลุ่มดัชนีน้ำตาลต่ำและกลุ่มสารหลอก อินเตอร์ลิวคิน-6 เพิ่มขึ้นอย่างมีนัยสำคัญภายหลังการออกำลังกายและในช่วงเวลาฟื้นสภาพในทั้งสามกลุ่ม (ทั้งหมด P < 0.05) นอกจากนี้ยังพบว่ามีความแตกต่างอย่างมีนัยสำคัญของอินเตอร์ลิวคิน-6ระหว่างกลุ่มสารหลอกและกลุ่มดัชนีน้ำตาลสูงใน 3 ชั่วโมงภายหลังการออกำลังกาย (P=.016) ความเข้มข้นของ ครีเอทีนไคเนสในซีรั่มในกลุ่มดัชนีน้ำตาลสูงมีค่าน้อยกว่ากลุ่มดัชนีน้ำตาลต่ำและกลุ่มสารหลอก ครีเอทีนไคเนสเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติในทุกช่วงเวลาในขณะที่ฟื้นสภาพในทั้งสามกลุ่ม (ทั้งหมด P < 0.05) ยกเว้น 1 ชั่วโมงภายหลังการออกกำลังกาย ในกลุ่มดัชนี (P = 0.31) แต่ไม่พบความแตกต่างอย่างมีนัยสำคัญระหว่างกลุ่มสำหรับครีเอทีนไคเนส

สรุปได้ว่า เครื่องดื่มที่มีดัชนีน้ำตาลต่ำ ที่เหมือนกับอาหารก่อนการออกกำลังกายทำให้เกิดการเปลี่ยนแปลง ต่อการตอบสนองของการอัเสบในการออกกำลังกายระยะยาว และสำหรับการออกกำลังกายด้วยแรงต้าน ดัชนีน้ำตาลสูง ขณะฟื้นตัวจากการออกำลังกายจะเกิดการเปลี่ยนแปลงต่อความเข้มข้นของอินเตอร์ลิวคิน-6

The dissertation titled

"The effect of glycemic index on interleukin-6 concentration in response to endurance and resistance exercise"

by

Sareh Hasani

has been approved by the Graduate School as partial fulfillment of the requirements for the Doctor of Philosophy Degree in Exercise Physiology of Srinakharinwirot University.

.....Dean of Graduate School

(Assoc. Prof. Dr. Somchai Santiwatanakul)

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Acknowledgements

I would like to express my deepest sincere gratitude and appreciation to my advisor. Asst. Prof. Dr. Supaporn Silalertdetkul, co-advisor, Dr. Witid Mitranun for their excellent instruction and supporting throughout this dissertation that enabled me to carry out this dissertation successfully. This dissertation was carried out at the department of Physical Education and Sport Sciences. I would like to thanks all those who have directly and indirectly contributed to this dissertation. My special thanks to Asst. Prof. Dr. Singha Chankha for their helps, encouragement me to complete this study. I would like to especially express my deepest gratitude to my family and all my friends for their love, sincere, intention, encouragement and understanding.

Sareh Hasani

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CHAPTER 1

INTRODUCTION

Strenuous, and prolonged exercise training induces a systemic inflammatory response, which is similar to trauma, infection or sepsis (Starkie; et al. 2001: 769-774). Inflammation is an important part of the immune response (Handschin; & Spiegelman. 2008: 463-469). Both heavy exercise, and poor nutrition could influences on immune function. To maintain immune function, athletes should eat a well-balanced diet that includes adequate protein, and carbohydrate sufficient to meet their energy requirements (Bishop; et al. 2001: 490-503). It has evidence that carbohydrate ingestion before, during, and after exercise can reduce inflammatory response (Nieman; et al. 2003: 1283-1290) , but regardless of existent knowledge about carbohydrate benefits in reducing inflammatory responses, there is no enough information about separate roles of each type of carbohydrate on inflammatory phase.

Interleukin-6 (IL-6) has been described as both a pro-inflammatory, and anti-inflammatory cytokine. IL-6 is an “inflammatory responsive” cytokine produced by various immune cells that is important in initiating the acute phase response and has some anti-inflammatory characteristics (Febbraio; et al. 2004: 42-55). It is clear that IL-6 play important role in the occurrence mechanism of emergency and chronic inflammation, keeping physiology balance of the body at the same time. IL-6 is elevated in response to muscle contraction, and this released is independent of muscle damage (Fischer. 2006: 1189-1194). Overall IL-6 is a regulator for glucose homeostasis, and lipolysis during exercise, and high IL-6 concentration is consistent with an enhancing lipolysis (Plewa. 1990: 193-206).

Exercise can induce inflammation by raising the levels of IL-6 (Nieman; et al. 2006: 398-403). Intensity, duration, and the muscle mass involved in the exercise are factors known to influence of IL-6 concentration (Ostrowski; Schjerling; & Pederson. 2000: 512-515). In prolonged exercise plasma IL-6 concentrations consistently increase >100-fold after 1 hour with 75% VO2max intensity (Cannon; Kluger; & Emst. 1983: 1235-1240; Pu; Tong; & Feng. 1996: 170-173; Espersen; Elbaek; & Emst. 1990: 395-400). The level of blood plasma IL-6 increases sharply and restored to the basic level 24 hours later following exercise (Plewa. 1990: 193-206). This increase in IL-6 could be related to the decrease in glycogen levels that occur during endurance exercise (Pedersen; & Hoffman-Goetz. 2008: 1379-1406). One the other hand, lengthening (eccentric) skeletal muscle contractions induce muscle damage,

and inflammation within muscle more than concentric contraction , in response to muscle damage, neutrophils and macrophages are mobilized into the circulation (Peake; et al. 2006: 514-521). The level of plasma IL-6 dramatically increased after eccentric exercise. IL-6 released in response to exercise may accordingly be more prominent in response to prolonged exercise compared with an intense but shorter bout of exercise, even if the peak IL-6 values are similar (Fischer. 2006: 6-33). However, although the IL-6 response was related to muscle damage, combination of mode, intensity and duration of the exercise determines the magnitude of the exercise-induced increase of plasma IL-6.

Carbohydrate (CHO) metabolism is a key factor that could influence on immune responses during exercise (Braun; & Duvillard. 2004: 645-650). Carbohydrate consumption before, during, and after exercise can attenuate stress hormone response, and improves exercise performance by enhancing blood glucose availability (Bishop; et al. 2002: 503-512; Febbraio; et al. 2003: 607-612; Nieman; et al. 2003: 1283-1290). Otherwise, CHO feeding before exercise cause a rapid increase in blood glucose, and insulin can cause hypoglycemia in some individuals at the start of exercise (Foster; Costill; & Fink. 1979: 1-5; Kuipers; Fransen; & Keizer. 1999: 227-231). Due to the strong evidence for enhancement of endurance performance and an attenuated stress hormone response via CHO supplementation, it is logical that a most researches have focused on the relations between CHO supplementation and immune function. Finally we can say that consuming CHO might be the most effective method for attenuating inflammatory responses to exercise. This point let us check different type of CHO, and their effect on inflammatory response.

As we know that glycemic index (GI) describes the difference by ranking CHO according to their effect on blood glucose levels compared with a reference food, which may be either glucose or white bread (Jenkins; et al. 1981: 326-366). This observation led to the investigation into the effect of different types, and structures of CHO and their comparison on exercise performance (Guezennec; et al. 1989: 45-50; Koivisto; Karonen; & Nikkila. 1981: 783-787). Numerous studies have suggested that a low-GI (LGI) meal consumed at different times, i.e. 1– 4 hours, prior to prolonged exercise could maintain higher blood glucose concentrations, decrease plasma lactate concentrations during exercise, and/or post-exercise, and cause a relative shift in substrate utilization from CHO to fat compared with a high-GI (HGI) pre-exercise meal (Wee; William; & Horabin. 1999: 393-399; DeMarco; et al. 1999: 164-170), but only some reported an enhancement in performance. Taken together the studies suggest there may be benefits to consuming LGI CHO before exercise, but to date, no research has indicated that consuming HGI foods before exercise negatively affects

endurance performance, even though some of them have indicated that HGI foods could increase performance, also some research suggested that consuming HGI CHO during recovery increased muscle glycogen synthesis in short time recovery time in resistance exercise (Thomas; Brotherhood; & Brand. 1991: 180-186). The discrepancy in the results in the literature may be due to the extent of the metabolic perturbation caused by the ingested CHO, which in turn may be related to the timing and amount of CHO ingested, as well as its GI.

On the other hand, the different type of CHO and exercise may have a various effects on immune function (Kirwan; et al. 2001: 849-855). Resistance training with high-force eccentric contraction causes more micro-tears in muscle, and more inflammatory responses than concentric contraction (Miles; et al. 2010: 1456-1464), also one of the most important aspects of recovery from resistance exercise, that can be influenced by nutrition is the synthesis of muscle glycogen to replace stores lost during exercise, and thus can be used as a model to study the influence of diet on the inflammation process. The inflammation might be increase with a high amount of CHO diet following a high-force eccentric contraction (Miles; et al. 2010: 1456-1464). On the other hand, some studied indicate that CHO sources with a moderate to high GI may enhance post exercise recovery (Burke; Kiens; & Ivy. 2004: 15-30). In prolonged exercise minimizing the glycemic and insulinemic response could sustain CHO supply during exercise. These responses could decrease the cortisol response, IL-6, TNF-α, and other inflammatory biomarkers (Bishop; et al. 2001: 490-503), also there is some evidences that a diet with high amount of glucose could increase pro-inflammatory cytokine (Kirwan; et al. 2001: 849-855). HGL diet is the exacerbation of glucose spike that occurs immediately after eating; this spike could alter glucose, and insulin dynamics during exercise (Pittas; et al. 2006: 2200-2209). In a pilot study we found that LGI beverage before sub-max exercise induced decrease the level of plasma IL-6 concentration, to compare with HGI and placebo. In totally low-GI meal may have potential benefits over a high-GI meal because of the promotion of the sustained CHO availability during exercise that its may decrease inflammatory responses, but although further research is needed to establish the connection between glucose kinetics of GI meal, IL-6 secretion, and other immune function both in body.

These data suggested that consuming food with different glycemic index could be effect on inflammatory responses in exercise. Despite the recent advances in researches are on the relation between immune suppression and CHO supplementation during prolong

exercise or CHO as meal before exercise (Miles; et al. 2010: 1456-1464). Therefore, knowing about that which type of CHO be able to reduce inflammatory responses in exercise, could guide the athletes for choosing beneficial nutrition to improve their performance. More research is necessary to elucidate the relationship between systemic inflammation, and GI diets in prolong exercise. Few studies, if any, have directly investigated the influence of a GI beverage on IL-6 response to prolonged exercise. There is clearly a pressing need to clarify the role of GI on IL-6 responses before prolonged exercise. Using an identical design, and subject population, this study aimed to examine the effect of a pre-exercise beverage with different GI on IL-6 responses to a sub-max exercise.

We can infer that over-release of the inflammatory cell during recovery after exercise may be an expression of decrease of body immune function. Evidence exists that large amount of glucose can decrease inflammation, and oxidative stress at rest in normal healthy individuals. On the other hand a HGI diet following a high-force eccentric arm exercise increased insulin resistance, and inflammation (Miles; et al. 2010: 1456-1464). The IL-6 response to carbohydrate ingestion during the early recovery period following intense resistance exercise is currently unclear. Therefore, knowing about that which type of CHO be able to reduce inflammatory responses during recovery in resistance exercise, could guide the athletes for choosing beneficial nutrition to reduce their damage. Few studies, if any, have investigated the influence of a GI beverage on IL-6 response during recovery from resistance exercise. We also examined the effect of a post-exercise beverage with different GI on IL-6 responses to intense resistance exercise.

Objective

Our objective of this study was to determine whether there are differences in plasma IL-6 concentration, and glucose metabolism between low and high GI beverage in sub-max exercise, and also during recovery from resistance exercise.

Research Hypotheses

Hypothesis 1: It was hypothesized that the concentration of plasma IL-6 would be lower in the low GI compared to high GI, and placebo groups in sub-max exercise.

Ho: $\mu_{LGI} = \mu_{HG\ I} = \mu_{placebo}$

Ha: $\mu_{LGI} < \mu_{HGI} < \mu_{placebo}$

Hypothesis 2: It was hypothesized that the concentration of plasma IL-6 would be lower in the high GI compared to low GI, and placebo groups during recovery from resistance exercise.

Ho: $\mu_{LG\ I} = \mu_{HGI} = \mu_{placebo}$

Ha: $\mu_{LGI} < \mu_{HGI} < \mu_{placebo}$

CHAPTER 2

LITERATURE REVIEW

Introduction

A greater understanding of inflammatory responses to exercise, and also especial nutrient dietary strategies could help to athletics to improving their performance. Physical activity with high intensity may induce an inflammatory response (Starkie; et al. 2001: 769-774). During and immediately following strenuous exercise pro-inflammatory cytokines are released. This literature will focus into the researches surrounding this area, beginning with the significance of inflammation in exercise, as there is evidence supporting a relationship between inflammatory response, and exercise, an overview of specific inflammatory cytokines such (IL-6) released in endurance and acute exercise. The exercise-induced IL-6 response is related to muscle damage (Bruunsgaard; et al. 1997: 833-841). The relationship between inflammatory response, and carbohydrate will be discussed; consuming carbohydrate has a beneficial effect on attenuate inflammatory responses to exercise (Nieman; et al. 2006: 394-403). Maintaining stable plasma glucose during prolonged exercise induces both advantageous for attenuating stress hormone, and cytokine responses (Nieman. 1998: 64-76; Bishop; et al. 2001: 490-503). Also one of the most important aspects of recovery that can be influenced by nutrition is the synthesis of muscle glycogen to replace stores lost during exercise (Ross; et al. 2010: 5-12). The GI will be discussed, indicating the importance of the quality of CHO, not only the quantity and also an overview of consume different GI as meal or beverage before, after, and during endurance, and resistance training will be discussed. Finally we want to know that, the amount, timing, and structure of CHO meal could have any effect on interleukin-6 concentration in endurance, and resistance exercise or not.

Interleukin- 6

IL-6 is an immune regulatory lymphocyte, with 23.1kDa (204aa) molecular weight (Friedland; et al. 1992: 2402-2408). IL-6 originates from mononuclear macrophages, fibroblasts, T cell, and B cell to stimulate immune response, e.g. during infection, and after trauma, especially burns or other tissue damage leading to inflammation in humans, it is encoded by the IL-6 gene (Ferguson; et al. 1988: 203-208). In addition, osteoblasts secrete IL-6 to stimulate osteoclast formation. Smooth muscle cells in the tunica media of many blood vessels also produce IL-6 as a pro-inflammatory cytokine. IL-6's role as an anti-inflammatory cytokine is mediated through its inhibitory effects on TNF-alpha and IL-1, and activation of IL-1ra and IL-10. IL-6 has been described as both a pro-inflammatory and anti-inflammatory cytokine, and an anti-inflammatory myokine (Petersen; & Pedersen. 2005: 1154-1162).

IL-6 is a modulator of bone resorption, a promoter of hematopoiesis, an important mediator of fever, and of the acute phase response (Fischer. 2006: 6-33). It is capable of crossing the blood-brain barrier (Banks; Kastin; & Gutierrez. 1994: 53-56). IL-6 is also essential for hybridoma growth, and is found in many supplemental cloning media such as briclone. Inhibitors of IL-6 (including estrogen) are used to treat postmenopausal osteoporosis. IL-6 is also produced by adipocytes and is thought to be a reason why obese individuals have higher endogenous levels of creatin reactive protein (CRP) (Bastard; et al. 1999: 2219-2222). Intranasally administered IL-6 has been shown to improve sleep-associated consolidation of emotional memories (Benedict; et al. 2009: 3629-3636). IL-6 is responsible for stimulating acute phase protein synthesis, as well as the production of neutrophils in the bone marrow. It supports the growth of B cells, and is antagonistic to regulatory T cells (Bruunsgaard; et al. 1997: 833-841).

On the other hand, IL-6 is considered as myokine, a cytokine produced from muscle, and is elevated in response to muscle contraction (Febbraio; et al. 2004: 42-55). It is significantly elevated with exercise, and precedes the appearance of other cytokines in the circulation. During exercise, it is thought to act in a hormone-like manner to mobilize extracellular substrates, and/or augment substrate delivery (Petersen; & Pedersen. 2005: 1154-1162). IL-6 has extensive anti-inflammatory functions in its role as a myokine. IL-6 was the first myokine that was found to be secreted into the blood stream in response to muscle contractions (Pedersen; & Febbraio. 2008: 1379-1406). The plasma IL-6 concentration is ~1 pg/ml or even lower in resting healthy subjects (Bruunsgaard; et al. 1997: 833-841; Ostrowski; et al. 1998: 889-894). In contrast, the plasma IL-6 concentration may

reach 10000 pg/ml in response to severe systemic infections (Friedland; et al. 1992: 2402-2408). The exercise-induced increase of plasma IL-6 occurs in an exponential manner, and the peak IL-6 level is reached at the end of the exercise or shortly thereafter.

IL-6 has serves dual purposes, acting as both a pro-inflammatory, and anti-inflammatory cytokine given different circumstances also has metabolic effect such as: increase lipolysis, increase glucose intake, and increase metabolism of the glucose. Physical activity and muscle damage could be increased the level of IL-6.

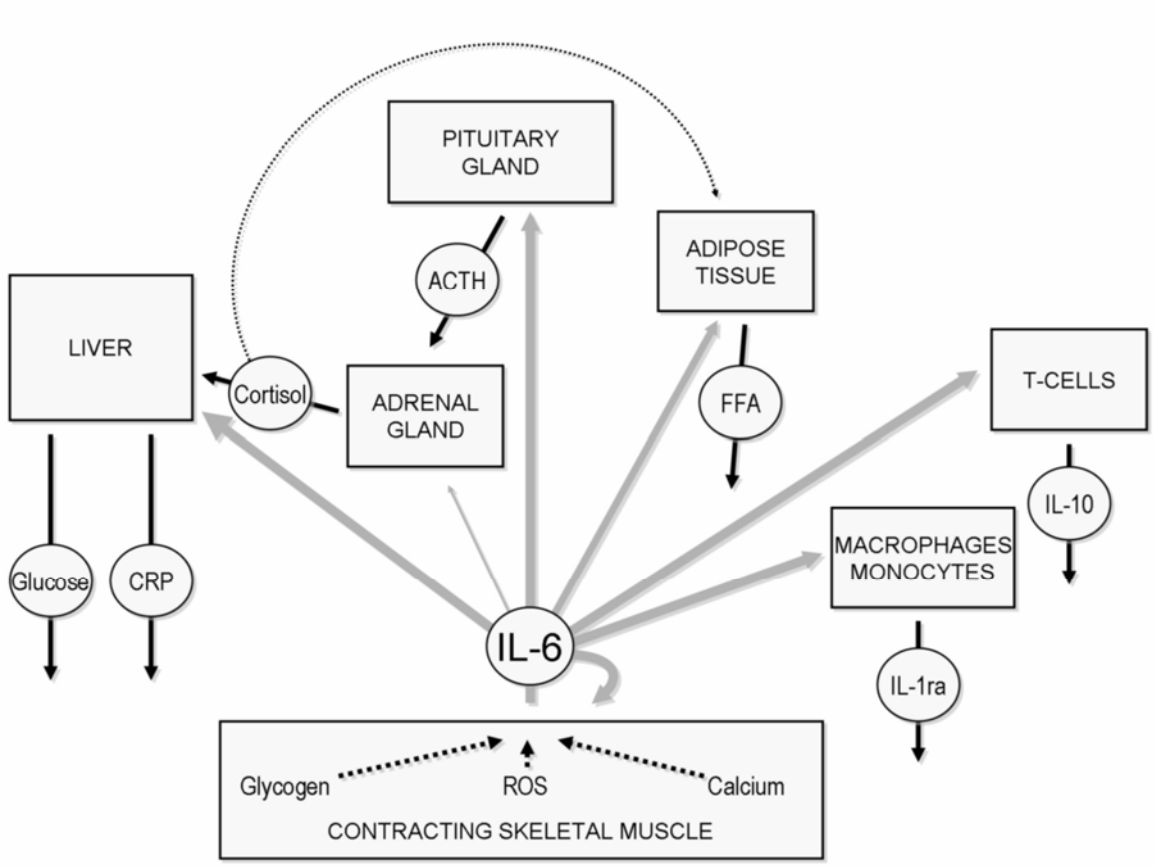

Figure 1 Possible effects of IL-6 released from contracting skeletal muscle in response to exercise (Fischer. 2006: 1189-1194).

IL-6 synthesis may link to several mechanisms: 1-Impaired glucose availability 2-Changes in calcium homeostasis, and increased formation of reactive oxygen species (ROS) (Fischer. 2006: 1189-1194). In liver, the circulating IL-6 may increase hepatic glucose output and production of C-reactive protein (CRP) (Nieman; et al. 2003: 1283-1290). In adipose tissue, IL-6 produced locally, and IL-6 may increase lipolysis. The synthesized IL-6 may act in a paracrine manner or be released into the circulation, thus able to induce systemic effects (Petersen; & Pedersen. 2005: 1154-1162). Via activation of the hypothalamic-pituitary-adrenal (HPA) axis, the circulating IL-6 may stimulate cortisol release, which may further enhance the lipolysis also in lymphocytes, macrophages, and monocytes, the circulating IL-6 may stimulate the production of IL-1ra and IL-10 (Bruunsgaard; et al. 1997: 833-841).

Interleukin-6 and exercise

Interleukin- 6 and endurance exercise

Systemic inflammation associated with endurance exercise is represented, partially, by elevations in blood concentrations of inflammatory cytokines such as TNF- α, IL-1β and particularly IL-6 (Northoff; Weinstock; & Berg. 1994: 167-171; Ostrowski; et al. 1998: 949-953). It is believed that certain types of exercise requiring high metabolic workloads cause cell injury, and the release of inflammatory cytokines (Drenth; et al. 1995: 1497-1503; Ostrowski; et al. 1999: 287-291; Weinstock; et al. 2002: 38-43).

The length of exercise and the amount of muscle mass engaged in the exercise are effective in increasing the level of IL-6 (Bacurau; et al. 2002: 423-431). It has been consistently demonstrated that the plasma concentration of IL-6 increases during endurance exercise. This increase is followed by the appearance of IL-1ra and the anti-inflammatory cytokine IL-10 (Nieman; et al. 2003: 1283-1290).

During endurance exercise our fuel comes from fat metabolism, blood glucose, and skeletal muscle glycogen stores. Lipolysis is the breakdown of stored fat in your body for energy, and glycogen is the storage form of carbohydrates in your body and is stored in high concentrations in the liver for when it is needed; IL-6 has been shown to promote lipolysis in adipose tissue, and glycogen breakdown in the liver (Petersen; & Pedersen. 2005: 1154-1162). These processes will help increase blood glucose levels. It is hypothesized that IL-6 is released from contracting skeletal muscle to help increase blood glucose by promoting lipolysis, and glycogen breakdown (Nieman; & Nehlsen-Cannarella. 1992: 121-148).

Circulation of IL-6 in the blood, could promote the production, and releasing the anti-inflammatory cytokines such as: IL-1ra and IL-10 (Petersen; & Pedersen. 2005: 1154-1162). Therefore, endurance exercise could induce an increase in circulating IL-6, and then IL-1ra, and IL-10 in sequential order, resulting in an overall anti-inflammatory response. There is some hypothesis that says this anti-inflammatory response is one of the ways that exercise can help reduce the risk of inflammatory related diseases like atherosclerosis, type II diabetes, and Alzheimer's disease (Petersen; & Pedersen. 2005: 1154-1162).

Cytokine change after 1 hour exercise at 75% of maximal oxygen consumption (VO2max) (Pu; Tong; & Feng. 1996: 170-173; Espersen; Elbaek; & Emst. 1990: 395-400). Most of studies demonstrated that after prolong exercise, the level of blood plasma IL-6 increases sharply, and restored to the basic level 24 hours later (Plewa. 1990: 193-206). During prolonged exercise plasma IL-6 concentrations consistently increase >100-fold post

exercise (Suzuki; et al. 2003: 348-355). Thus, the 8000-fold increase of plasma IL-6 following a 246 km “Spartathlon” race represents an atypical, and extreme response (Margeli; et al. 2005: 3914-3918). Elevated plasma levels of IL-6 have been associated with increased sensation of fatigue at rest. Otherwise the release of the IL-6 might be confined to muscle or other organ’s macrophage in exercise, and put forward IL-6 was the main factor to induce exercise acute response (Northoff; Weinstock; & Berg. 1994: 167-171). From above, we can infer prolonged exercise is capable of elevating levels of circulating IL-6 that over-release of the inflammatory cell during endurance exercise, and recovery after exercise may be an expression of decrease of body immune function that the coach, and athletes should pay attention to the research in this aspect.

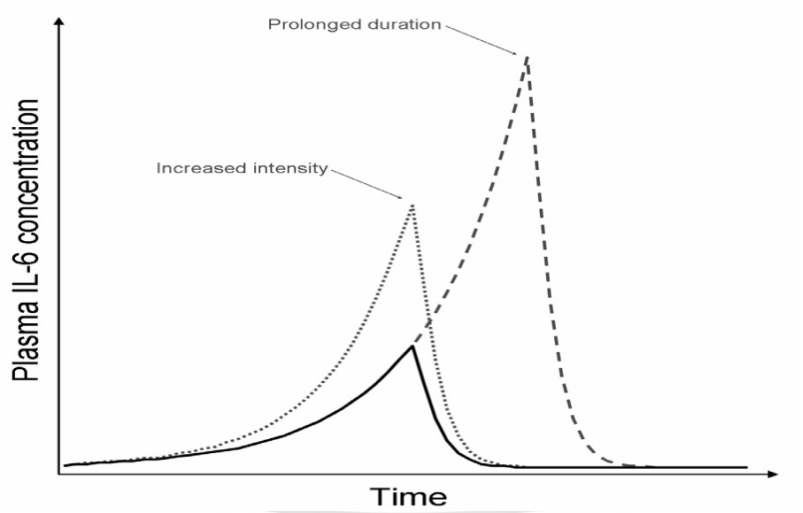

Figure 2 The effect of exercise duration and intensity on the plasma IL-6 level (Fischer. 2006: 6-33).Plasma IL-6 increases in a non-linear over time, and keep to the peaks shortly after exercise (solid line). When exercise intensity increases, plasma IL-6 increase faster resulting in a higher peak plasma IL-6 level (dotted line). When exercise duration is extended, the peak plasma IL-6 occurs later but is also augmented (dashed line).

Interleukin-6, and resistance exercise

A few studies have looked at the effects of resistance training on circulating cytokine levels (Brown; et al. 1997: 215-222; Lavender; & Nosaka. 2006: 619-626; Miles; et al. 2007: 507-520). The level of IL-6 in the blood would be rising rapidly, and immediately after resistance exercise, (Bruun; et al. 2003: 535-546). Several studies have consistently reported that the plasma IL-6 concentration increases in response to acute exercise. Although the plasma concentration of several other cytokines may be affected by exercise, but IL-6 increases more dramatically than any other cytokine investigated to date (Ostrowski; et al. 1999: 287-291; Pedersen; & Hoffman-Goetz. 2000: 1055-1081; Northoff; Weinstock; & Berg. 1994: 167-171). Following resistance exercise, the basal plasma IL-6 concentration may increase up to 100 fold, but less dramatic increases are more frequent. Of note, the exercise-induced increase of plasma IL-6 is not linear over time; repeated measurements during exercise show an accelerating increase of the IL-6 in plasma in an almost exponential manner (Fischer; et al. 2004: 1189-1194; Ostrowski; et al. 1998: 949-953). Furthermore, the peak IL-6 level is reached at the end of the exercise or shortly thereafter, followed by a rapid decrease towards pre-exercise levels (Fischer; et al. 2004: 1189-1194; Ostrowski; et al. 1998: 949-953).

Importantly, there are different types of muscle actions: concentric, eccentric, and isometric. The eccentric actions occur during the lowering phase of any weightlifting exercise, and are defined as the muscle actions where the muscle lengthens because the contraction force is less than the resistive force (Hurman; et al., 2000). Nosaka and Clarkson (1996: 9131-9196) hypothesized eccentric exercise in untrained muscle will induce damage to the muscle. In response, a series of local acute inflammatory responses will follow to heal the damaged tissue. This damage, and repair process will also induce a systemic inflammatory response. The systemic inflammatory response is called the acute-phase response (MacIntyre; et al. 2001: 180-186). A sign of muscle damage is the increase or appearance of enzymes in muscle tissue (Brown; et al. 1997: 215-222). One of the main enzymes usually released into circulation is creatine kinase (CK); it is a protein that found primarily in muscle tissue (Lavender; & Nosaka. 2006: 619-626). The level of increase of CK can be verify from person to person, and also depends on the level of muscle damage, and the intensity of the exercise (Evans; & Cannon. 1991: 99-125). CK increases with muscle damage, and/or inflammation 4-5 days following a bout of exercise; therefore it can be used as an assessment of damage, and inflammation to muscle tissue with exercise (Malm; et al. 2004: 983-1000).

Resistant training, involving eccentric actions induces muscular damage to a higher extent than concentric actions; it now has become clear that eccentric exercise is not associated with more marked increases of plasma IL-6 than compared to exercise involving concentric muscle contractions (Fischer; et al. 2004: 1189-1194). Thus, muscle damage is not required in order to increase plasma IL-6 during exercise. Rather, eccentric exercise may result in a delayed peak, and a slower decrease of plasma IL-6 during recovery (Hellsten; et al. 1997: 239-248; MacIntyre; et al. 2001: 180-186; Willoughby.; McFarlin; & Bois. 2003: 15-21). In contrast, the IL-6 response is sensitive to the exercise intensity, which again indirectly represents the muscle mass involved in the contractile activity (Ostrowski; Schjerling; & Pederson. 2000: 512-515). Further studies may discover other sites contributing to the IL-6 in the circulation in response to exercise.

Overall, resistance exercise has been associated with transient suppression of immune function, potentially adverse effects on cellular distribution of immune cells, and elevation in the production of cytokines that exert pro inflammatory effects. The acute effects of resistance exercise on inflammation are summarized in Table 1.

Table 1 Studies evaluating the acute effect of a resistance training bout on inflammatory markers. IL; interleukin; TNF; tumor necrosis factor, 1RM; maximal dynamic strength, Ex; exercise.

Author	Population	Exercise test protocol	Cytokines	Results
Phillips et al. (2010)	14 active men	major muscle groups of upper and lower body. Low intensity: 2X12 repeats 65%1RM High intensity: 2X8Reps 85%1RM	IL-6	IL-6 increased Post-Ex. The Low intensity protocol resulted in the highest IL-6 compared to the high intensity.
Buford et al. (2009)	24 active women	Squat, leg press and leg extension. 3X10 repeats 80%1RM	IL-6 IL-8 TNF-α	There was mRNA up-regulation for TNF-α, IL-6 and IL-8 Post-Ex
Uchida et al. (2009)	35 men	4X20 repeats 50%1RM 5X11 repeats 75%1RM 3X10 repeats 90%1RM 3X10 repeats 110%1RM	IL-1β IL-6 IL-10	No differences in cytokine responses among different intensity protocols.
Peake et al. (2005)	10 untrained men	Sub-maximal: 10X60rep10%1RM elbow flexor of one arm Maximal: 10X3 repeats 100%1RM elbow flexor of the opposite arm.	IL-6 IL-10 TNF-α CRP	IL-6 was elevated 3 h Post-ex after Sub-maximal. The rest of the cytokines and CRP remain unchanged after Ex.
MacIntyre et al. (2001)	12 active men	30X10 repeats of eccentric right leg	IL-6	IL-6 increased compared to Pre-Ex.
Smith et al. (2000)	6 active men	Bench and leg press 4×12 repeats 100% 1 RM	IL-6 IL-0	IL-6 was elevated until 72 hrs after Ex. IL-10 was elevated at 6 days after Ex.

Glucose ingestion, exercise and Interleukin- 6

There is evidence that the elevation in IL-6 observed in response to intense exercise is in part caused by muscle production of this cytokine (Steensberg; et al. 2003: 631-638; Starkie; et al. 2001: 769-774; Steensberg; et al. 2001: 633-639). It has been shown that myocytes produce IL-6 in response to muscle contraction (Steensberg; et al. 2003: 631-638) and it has been proposed that the cytokine plays a role in substrate mobilization and/or regulation (Bishop; et al. 2002: 503-512; Steensberg; et al. 2003: 631-638;). Pedersen; Zacho and Febbraio (2003: 1337–1362) also reported that physiologic concentrations of IL-6 induce lipolysis. As a consequence, it might be implied that the blunted IL-6 production that commonly occurs during exercise in which CHO is provided is a result of substrate availability, that is, with exogenous substrate delivery during exercise, the strain placed on endogenous stores may be reduced, resulting in an attenuated stress hormone response, and reduction in IL-6 production (Nieman. 1998: 64-76). These effects may directly or indirectly affect stimulation of the immune system. These findings support the notion that CHO serves to down regulate the pro-inflammatory response to exercise, and that there is a concomitant reduction in anti-inflammatory cytokine secretion (Ansley; et al. 2009: 186-194). The interaction between the hypothalamic-pituitary-adrenal axis, immune cell function and proliferation, substrate availability, and pro-inflammatory cytokine production presents a complex area for examination (Figure 3). It may be that IL-6 produced by the immune system has a separate biological function from that produced by active muscles.

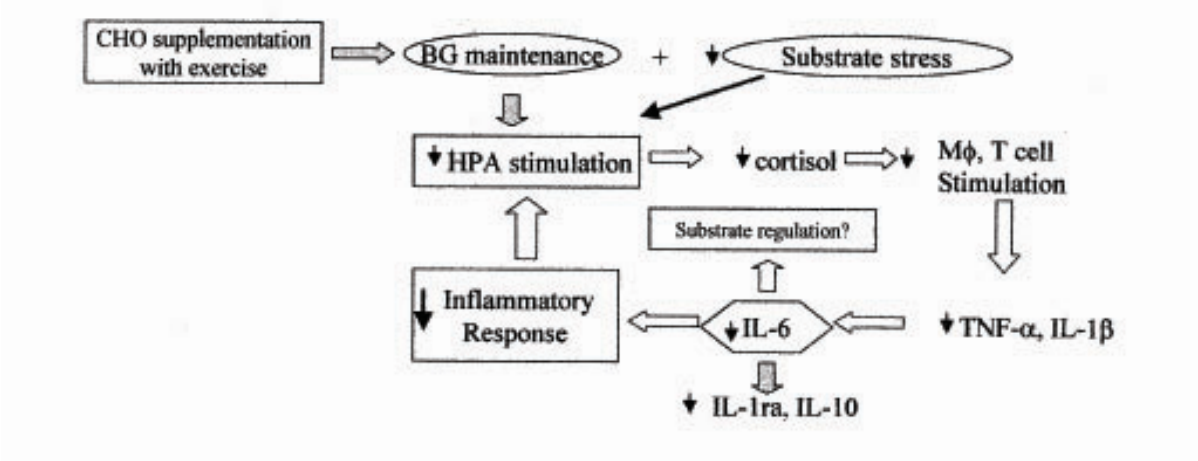

Figure 3 Carbohydrate delivery and stress response to exercise (Braun; & Duvillard. 2004: 645-650). Ingestion CHO during exercise can sustain glucose availability, and reduce substrate stress. It causes an attenuated stimulation of the HPA axis and lower cortisol production. This may reduce perturbations in immune status, leading to lower IL production, and may influence substrate use. BG, blood glucose; CHO, carbohydrate; HPA, hypothalamic-pituitary-adrenal. axis; IL, interleukin; TNF, tumor necrosis factor.

Based on these findings, it is possible that CHO supplementation or a high-CHO diet aids in limiting the production of pro-inflammatory cytokines (Table 2). A blunted production of anti-inflammatory cytokines (IL-1ra and IL-10) may be secondary to this effect. These findings may be important, particularly when exercise involves heavy eccentric loading, because it has been proposed that a hyper inflammatory response (as may occur with infection, and heavy eccentric exercise), may lead to delayed immunosuppression (Smith. 2000: 61-67; Biffl; et al. 1996: 647-653).

Ultimately, in response to endurance exercise or resistance exercise in which muscle damage results, pro- inflammatory cytokines are produced. CHO consumed as maintainer blood glucose in stable level decrease cytokine response to exercise.

Table 2 Carbohydrate influence on cytokine response to acute exercise (relative to placebo or control condition).

Reference	Mode	Intensity	Duration	Cytokines	After exercise	Recovery	Treatment
Bacurau et al. (2002)	Cycling	90% AT	2 h	IL-1 IL-2 IL-6	Increased Increased Increased	NA NA NA	Feedings
Bishop et al. (2002)	Soccer drills	_	90 min	TNF-α IL-6	ND ND	ND Decreased	Feedings
Bishop et al. (2001)	Cycling	60% vo2 max and time trial	90 min	IL-6 IL-1ra IL-10	ND ND ND	Decreased Decreased Decreased	Control diet
Nehlsen-Cannarella et al. (1997)	Running	70%	2.5 h	Total IL-6 Biological IL-6	Decreased Increased	Decreased ND	Feedings
Nieman et al. (1998)	Running, Cycling	75%	2.5 h	IL-6 IL-1ra	Decreased Decreased	Decreased Decreased	Feedings
Nieman et al. (2003)	Marathon	_	Varied	IL-6 IL-8 IL-10	ND ND Decreased	ND Increased Decreased	Feedings
Nieman et al. (2001)	Resistance training	_	2 h	IL-6 IL-8 IL-10	ND ND ND	NA NA NA	Feedings

AT; anaerobic threshold, IL; interleukin, NA; not available, ND; not different versus control, TNF; tumor necrosis factor.

Glycemic index

Glycemic index (GI) is a ranking of carbohydrates on a scale from 0 to 100 according to the extent to which they raise blood sugar levels after eating (Febbraio; et al. 2000: 1845-1851). Essentially, the GI is designed to indicate the overall rate of digestion, and absorption of the CHO in a food. Foods with an HGI (>70) are generally digeste, and absorbed quickly, whereas foods with an LGI (<55) are digested and absorbed more slowly. For a comprehensive list of up-to-date GI values of common foods the reader is directed. The GI of a food can be influenced by the physical and chemical characteristics of the food (Foster; Costill; & Fink. 1979: 1-5). If the GI of CHO influences the rate at which CHO elicits a blood glucose response, feeding CHO of differing GI before, during, and after exercise might influence sport performance.

Glycemic index and endurance performance

It is widely accepted that CHO ingestion before, during, and after endurance exercise improves performance. However, CHO feeding before exercise remains a contentious issue, because a rapid increase in blood glucose, and insulin can cause hypoglycemia in some individuals at the start of exercise (Foster; Costill; & Fink. 1979: 1-5; Kuipers; Fransen; & Keizer. 1999: 227-231). This observation led to the investigation into the effect of different types, and structures of CHO on exercise performance (Guezennec; et al. 1993: 224-231; Guezennec; et al. 1989: 45-50; Koivisto; Karonen; & Nikkila. 1981: 783-787), and to the comparison of the effects of differing GI on endurance performance. These investigations were based on the premise that consuming LGI CHO before exercise would minimize the glycemic and insulinemic response seen with HGI CHO and result in a sustained CHO supply during exercise. The studies investigating the effects of the GI of CHO fed before exercise can be divided into two categories: GI of CHO ingested 1 hour or less before exercise (Table 3), and more than 1 hour.

Totally according the knowledge athletes should choose LGI CHO for pre exercise meals. However, although feeding LGI foods or meals an hour or less before exercise results in higher blood glucose concentrations during exercise and difference in time to exhaustion.

Table 3 Studies of glycemic index and pre exercise CHO ingested 1 hour or less before exercise.

Study	**Subject**	**Exercise protocol**	**CHO feeding**	**Metabolic response**	**Performance**
Febbraio et al. (2000)	8 trained Men	Cycle at 70% VO2peak for 120 + 30 mins	LGI, HGI control 30 mins before exercise	HGI produced significantly higher blood glucose after ingestion and lower blood glucose after exercise.	No difference in total work performed
Arcin et al. (2001)	10 trained men	Cycle at 80% VO2max for 60 mins	LGI , HGI , Control- every 30 mins for 3 h, until 10 mins before exercise	HGI produced a decrease in blood glucose 30 mins after initiation of exercise.	Not measured.
Moore et al. (2010)	10 trained	40-km time trial	LGI , HGI 45 mins before exercise.	HGI produced higher blood glucose and insulin after ingestion.	Time trial was faster in LGI.
DeMarco et al. (1999)	10 trained male	Cycle at 70%VO2 max for 2 hours	LGI, HGI, control 30 mins before exercise	HGI produced higher blood glucose after ingestion. After 120 min of exercise blood glucose were higher in LGI.	Time to exhaustion longer with LGI.
Sparks et al. (1998)	8 trained men	Cycle at 70% VO2peak for 50 mins	LGI, HGI, control 45 mins before exercise	HGI produced higher blood glucose after ingestion but lower blood glucose levels after exercise.	Not difference.

LGI, low glycemic index; HGI, high glycemic index

Table 3 (continued)

Study	Subject	Exercise protocol	CHO feeding	Metabolic response	Performance
Febbraio et al. (1996)	6 trained men	Cycle at 70% VO2peak for 120 mins	LGI, HGI, control- 45 mins before exercise	HGI produced higher blood glucose post ingestion.	Not difference.
Thomas et al. (1994)	6 trained men	Cycle to exhaustion at 65–70% VO2max	LGI, HGI, control- 60 mins before exercise	LGI foods produced lower glucose at rest but higher blood glucose and higher FFA at the end of exercise.	Not difference.
Thomas et al. (1991)	8 trained men	Cycle to exhaustion at 65–70% VO2max	LGI, HGI, control- 60 mins before exercise	LGI produced lower glucose at rest but higher blood glucose, FFA higher at the end of exercise.	Time to exhaustion was longer with LGI.
Kirwan et al. (2001)	6 active men	Cycle at 60% VO2max until exhaustion	LGI, HGI, control- 45 mins before exercise	HGI produced higher blood after ingestion. At 60 and 90 min LGI reduced higher blood glucose.	Time to exhaustion was longer in LGI.

LGI, low glycemic index; HGI, high glycemic index

Glycemic index and post exercise nutrition

One of the most important aspects of recovery that can be influenced by nutrition is the synthesis of muscle glycogen to replace stores lost during exercise. The amount, timing, and frequency of CHO ingestion have been shown to affect glycogen synthesis (Jentjens; & Jeukendrup. 2003: 117-144). Consuming CHO immediately after exercise results in higher glycogen levels 4 hours after exercise than if CHO ingestion is delayed by 2 hours (Ivy; et al. 1988: 1480-1485). The highest rates of muscle glycogen resynthesize have been reported when CHO is fed every 15 mins to provide 1.0–1.8 g · kg BM over a 2 to 4 hours period immediately after exercise (Piehl Aulin.; Söderlund; & Hultman. 2000: 346-351; Van Hall; Shirreffs; & Calbet. 2000: 1631-1636). This suggests that when the interval between exercise sessions is short CHO should be consumed as soon as possible after exercise to maximize recovery. However, when longer recovery times are available the consumption of CHO immediately after exercise is not as important. As long as 7–10 g/kg BM of CHO is consumed over 24 hours muscle, and liver glycogen will be replaced over this time (Coyle. 1991: 29-52). Glycogen synthesis, and storage are largely influenced by insulin and a rapid supply of glucose substrate. Therefore, CHO sources with a moderate to high GI may enhance post exercise recovery (Burke; Kiens; & Ivy. 2004: 15-30). Consuming LGI CHO led to a decline in muscle glycogen from baseline values, and this decline was greater than after consuming HGI CHO (Kiens; & Richter. 1996: 47-53).

Taken together, it would seem that if recovery periods are short (i.e., <8 hours), CHO is the most important nutrient, and should be consumed immediately after the exercise session. HGI CHO foods tend to be less bulky, and more energy dense than LGI foods. HGI CHO should be consumed during this period, especially when HGI CHO elicits a higher insulin response, and is associated with increased muscle glycogen resynthesize. When longer recovery periods are available there seems to be a role for a greater variety of nutrients, but consuming adequate CHO for muscle glycogen synthesis is still important.

Glycemic index and Interleukin- 6

Food consumption and inflammation is a hot topic, as inflammation may be induced or decreased by food intake (O'Keefe; Gheewala; & O'Keefe. 2008: 249-255). Some theory indicates that LGI CHO could decrease level of IL- 6 by: 1- Minimizing the hypoglycemia that occurs at the start of exercise 2- Increasing the concentration of fatty acids in the blood 3-

Increasing fat oxidation, and reduces reliance on carbohydrate fuel (Wallberg; Ekblom; & Mattsson. 2009: 19-29). Advocates of low CHO diets insist that they result in decreased plasma glucose, a blunted insulin response, and decreases in CRP (Forsythe; et al. 2008: 65-77). To understanding of how a LGI diet could decrease inflammation, a look at the pro-inflammatory effects of a HGI diet is useful (Pittas; et al. 2006: 2200-2209).

Summary

Systemic inflammation associated with exercise is represented, partially, by elevations in plasma concentrations of inflammatory-related cytokines such as TNF- α, IL-1β, and IL-6 (Ostrowski; et al. 1998: 949-953 Smith. 2000: 61-67). Also most of studies demonstrated that IL-6 secreting amounts increased obviously in endurance exercise when doing 60 minutes at 70-75% VO2 max intensity (Ben; & Weksler. 1992: 525-531; Pu; Tong; & Feng. 1996: 170-173; Espersen; Elbaek; & Emst. 1990: 395-400) and also in resistance exercise, IL -6 would be rising rapidly and immediately after exercise.

Many investigators have studied the effects of CHO supplementation, and dietary control on the cytokine response to exercise. It has been reported previously that carbohydrate (CHO) ingestion attenuates elevations in plasma IL-6 during both prolonged running (Nehlsen; et al. 1997: 1662-1667; Nieman. 1998: 64-76), and cycling (Nieman. 1998: 64-76). CHO supplementation during sustained exercise may assist in reducing infection risk is yet to be confirmed. However, based on attenuated cortisol and pro inflammatory cytokine production during and after acute exercise when CHO has been provided, it may be beneficial for immune function to supply the body with exogenous CHO. CHO feeding before, during, and after recovery is now generally accepted as a means of improving endurance performance. However, CHO feeding before exercise remains a contentious issue, because a rapid increase in blood glucose, and insulin can cause hypoglycemia in some individuals at the start of exercise (Foster; Costill; & Fink. 1979: 1-5; Kuipers; Fransen; & Keizer. 1999: 227-231). In recovery CHO is the most important nutrient, and should be consumed immediately after the exercise session (Ivy; et al. 1988: 1480-1485). Most studies suggest that consuming LGI CHO before exercise results in a favorable metabolic profile during

exercise, but only some report an enhancement in performance (Guezennec; et al. 1993: 224-231; Guezennec; et al. 1989: 45-50; Koivisto; Karonen; & Nikkila. 1981: 783-787).

On the other hand, LGI CHO could maintain blood glucose in steady stage by increasing fat oxidation, and decrease reliance on carbohydrate fuel. It help to reducing level of IL- 6 In totally low-GI meal may have potential benefits over a high-GI meal because of the furthering of the sustained glucose availability during exercise that it may reduce IL-6 and other inflammatory responses. This observation led to the investigation into the effect of different types and structures of CHO feeding before endurance exercise, and also at resistance training on immune function, and finding the comparison between them.

CHAPTER 3

Study1: Effect of glycemic index on plasma Interleukin 6 in sub-max exercise

Introduction

The inflammatory response is a generalized immune response to tissue damage or illness (Smith et al., 2000). The inflammatory response is a generalized immune response to tissue damage or illness (Smith. 2000: 61-67). Consuming carbohydrate (CHO) might be the most effective method for attenuating inflammatory responses to exercise. Ingestion CHO during exercise can sustain glucose availability, and reduce substrate stress (Nieman; et al. 2003: 1283-1290). IL-6 is increased in glycogen-depleted muscles, (Steensberg; et al. 2001: 633-639), and it is a factor in endogenous glucose production, and hence controls glucose homeostasis (Febbraio; et al. 2004: 42-55). When glucose is ingested during the course of exercise, glycogen levels will not decrease as fast when compared to placebo ingestion, and glucose production may, therefore, be minimal. IL-6 is not released as much with carbohydrate ingestion when compared to placebo during exercise sessions, indicative of its role in glucose homeostasis (Febbraio; et al. 2003: 607-612). This observation led us to investigate the effect of different types, and structures of CHO feeding in the body through the use of the glycemic index (GI), which is a measure of the rate of glucose entry into the blood.

Lower GI foods result in a smaller deviation in blood glucose, hence a lesser dependence on insulin to uptake glucose in the cells. It is hypothesized that the LGI diet works by decreasing glucose-insulin dynamics, resulting in less oxidative damage and decreased prevalence of IR-inducing inflammation (Nieman; et al. 2003: 1283-1290). In endurance exercise minimizing the glycemic could sustain CHO supply during exercise that it could decrease the cortisol response, IL-6, and other inflammatory markers (Bishop; et al. 2001: 490-503).

The purpose of this study was to determine whether there are differences in plasma interleukin- 6 concentrations and glucose metabolism between low and high GI beverage in sub-max exercise. Measured variables included interleukin-6 (IL-6), creatine kinase (CK),

and glucose. It was hypothesized that all dependent variables would be lower in the LGI compared to HGI diet groups, and placebo after sub-max exercise. More knowledge about inflammation, and glucose metabolism in exercise allow investigators to more effectively direct individuals towards proper diet for improving performance in athletes.

Methodology

Subjects

Ten endurance-trained male runners volunteered to participate in this study. They were approved by the Tehran University Ethical Committee and complete a medical history questionnaire to screen for contraindications that were excluded them from participation in the study, and subjects were excluded based on the following criteria: acute infections, recent oral surgery, injuries, and certain medications known to influence cytokine production such as non-steroidal anti-inflammatory medications or medical conditions, and if any medication had been taken during the 6 weeks prior to the study, and if symptoms of upper respiratory infection had been experienced in the 6 weeks prior to the study, and if symptoms of upper respiratory infection had been experienced in the 4 weeks prior to the study. Moreover, at the time of the study, all subjects were involved in normal training, and were accumulated at least 50 km of running distance per week. Subjects were asked to refrain from alcohol consumption 24 hours prior to sample collection.

Research Design

This study was a counterbalanced cross-over design, and the orders of the three trials were randomized, separated by at least 14 days. Subjects were instructed to keep their daily exercise to minimum. Each subject kept 3 days diary of their dietary intake before the main trial. They were required to repeat the same diet before each main trial to minimize the variation in muscle, and liver glycogen concentrations. Before each trial, they were reported to the laboratory after 12 hours of an overnight fast. This was to ensure an empty stomach, and to minimize the effect of a previous meal on the gastric emptying rate of the test meals.

Exercise familiarization

Subjects reported to the laboratory on four separate occasions. On the first visit, they were completed the medical history questionnaire, and have any questions answer prior to beginning any testing. Resting blood pressure, and pulse measurements were taken follow by anthropometric measurements of body mass and height. Body fat was measured using by caliper model 1127 Japan, and following body composition screening, subjects were completed a maximal oxygen consumption (VO2max) test, using the Bruce protocol treadmill test to predict rate of maximal oxygen consumption (VO2max).

On the day of the main trial, between four and seven days after the first visit the subjects were come to the laboratory at about 8:00 am after an overnight fast of 12 hours. After collection of the baseline blood samples the participants were consumed either the GI beverage High-GI (1 g of glucose/kg body mass in 400 ml water, GI = 83), Low-GI (1 g of fructose/kg body mass in 400 ml water, GI = 36) or placebo (an equal volume of flavor- and color-matched artificially sweetened placebo). 45 mins after consuming the beverage they were started training: A standardized 5 mins warm-up at 60% VO2 max was performed after the 45 mins resting period. Then subjects were run at a fixed speed of 70% -75%VO2 max for 1 hour. All of the trials were performed under similar conditions of barometric pressure, temperature, and relative humidity. No food was allowed until after the final blood sample was taken also their body mass were measured at the first of each trial.

Baseline Measurements

Blood pressure: Blood pressure, and resting pulse measurements was taken using an Omron IntelliSense® Professional Blood Pressure Monitor (Model HEM-907XL, Health Check Systems, Inc., Brooklyn, NY) after participants sit quietly for ten minutes.

Body mass and body fat percentage: Body mass was measured at the first of each trial by using a coin weight scale machine model fv1201 Japan. Excess clothing such as coats, sweatshirts, and shoes were be removed, but no other clothing were removed, and body height was recorded using a stadiometer (seca® 240 wall-mounted) , also the body fat

percentage was measured using caliper model 1127 Japan with 3 point Jackson Pollock (Jackson& Pollock,1985) formula. The chest, abdomen, and thigh sites were used to calculate the body fat percentage. The chest skin fold was a diagonal fold just in front of the armpit and in line with the nipple. The abdominal fold was a vertical fold approximately 1 inch to the right of the umbilicus and 1/2 inch below. The thigh fold was another vertical fold in the middle of the thigh, halfway between the hip crease, and the top of the kneecap.

Maximal oxygen consumption (VO2max)

The VO2max test was measured via a modified Bruce protocol for running on treadmill (Techno gym Excite 700i). The ramp-style test began at a 10% grade and 2.7 km/hr, and both speed, and grade were increased every three minutes (Stage 2 = 4 km/hr, 12% grade; Stage 3 = 5.5 km/hr, 14% grade; Stage 4 = 6.8 km/hr, 15% grade; Stage 5 = 8 km/hr, 15% grade; Stage 6 = 8.9 km/hr, 15% grade). Subjects wore a polar with coded transmitter 31 (Kemple, Finland) for monitoring their heart rate. Oxygen uptake was calculated from measures of ventilation via oxygen and carbon dioxide analyzers (Cortex METALYZER® 3B). Results were presented as ml/kg/min (mls of oxygen per kilogram of body weight per minute). The athlete was considered to have reached their VO2max if several of the following occurred: a plateau or 'peaking over' in oxygen uptake, maximal heart rate was reached, attainment of a respiratory exchange ratio of 1.15 or greater, and volitional exhaustion.

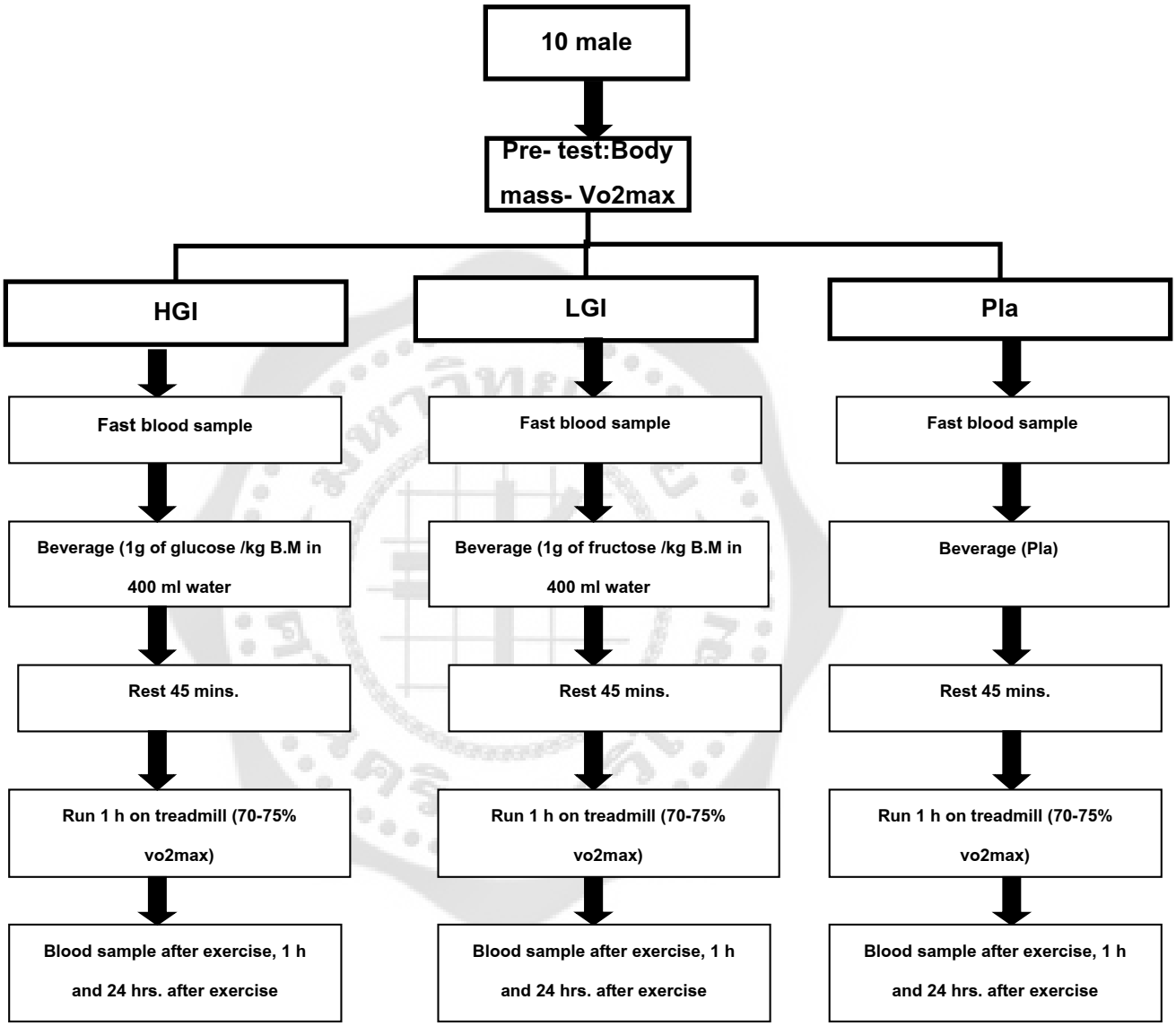

Figure 4 Represented chart of the experimental procedures, showing exercise bouts. H-GI; 1g of glucose /kg B.M in 400 ml water, L-GI; 1g of Fructose /kg B.M in 400 ml water, Pla; placebo.

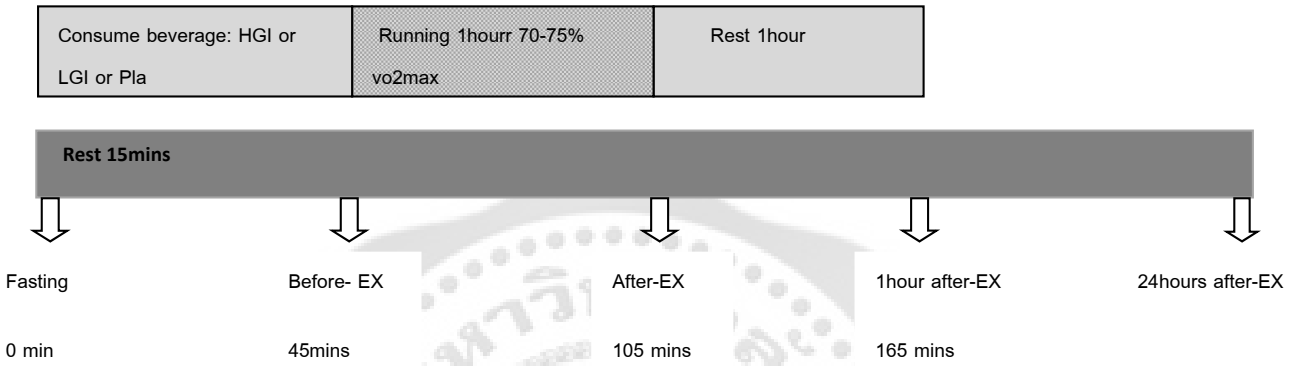

Figure 5 Schematic representations of the experimental procedures, showing exercise bout.

⇨ : Blood sample taken for immune assessment

H-GI: 1g of glucose /kg B.M in 400 ml water

L-GI: 1g of fructose /kg B.M in 400 ml water

Pla: placebo

Blood analyses

10 ml venous blood was drawn from an antecubital vein in the forearm at each time points: 1- Fast blood sample (F.B.S), 2 - Pre-exercise, 3- Immediately post-exercise, 4- 1 hour after exercise, 5- 24 hours after exercise. Blood samples were drawn into a vacuum tube with clot activator and serum separator for collection of serum to analyze glucose, and CK. Plasma was separated immediately from blood cells by centrifugation at 2150 g at +4ºC for 15 mins, and was transferred into Eppendorf tubes and immediately was frozen at −80°C until later analysis.

Plasma IL-6 was measured by high-sensitivity Enzyme-linked immunosorbent assay (ELISA) kit from R&D systems (Minneapolis, MN, USA). Its procedures were followed according to the kit specifications. Samples were diluted when necessary to ensure that the measurement fall within the range of the standard curve, and creatine kinase (CK) was measured by the SYNCHRON® System(s) (Beckman Coulter, Inc.USA). Serum glucose was measured by BIOSEN C (EKF Diagnostic GmbH, West Germany) analyzer.

Statistical analyses

Samples size were calculated with a software that developed by Dr. David Schoenfeld with support from the MGH Mallinckrodt General Clinical Research Center. A total of 10 subjects were entered in this two-treatment crossover study. The probability was 84 percent that the study was detected a treatment difference at a two-sided 0.05 significance level, and difference between treatments was 1.500 units.

All collected data were presented as mean and standard deviation (Mean ± SD). Before hypotheses tests, normality of data was checked out using Shapiro-wilk test as the number of observations. Box's M and Levene's Tests were used to check out homogeneity of variances as well as equality of error variances between groups. As this study employed a repeated measure design, therefore, Mauchly's test was used to check sphericity assumption which refers to the condition where the variances of the differences between all possible pairs of groups were equal and then appropriate adjustments in the degrees of freedom was made. Repeated measures 5 (measurements: F.B.S , pre-exercise, post-exercise, 1 hour after exercise, and 24 hours after exercise × 3 (groups: H-GI, L-GI, and placebo) ANOVAs were applied to examine the main effects of independent variables (HGI, L-GI and placebo groups) on the IL-6, CK and glucose concentrations . Finally, significant within-group effects in all analyses was followed up by paired *t*- tests with an appropriate Bonferroni correction, and one-way ANOVAs and LSDs follow up tests were applied for significant between group effects. In all the above designs, H-GI, L-GI, and placebo were considered as within-group and between-group factors, respectively. Statistical significance was sat at an alpha of $p < .05$. The data were analyzed using the statistical package SPSS, PC program, version 19.0 (SPSS Inc., USA).

Results

Ten healthy subjects participated in this study, and completed 3 (H-GI, L-GI, and placebo) sessions of endurance exercise (running at a fixed speed of 70% -75%VO2 max for 1 hour). The descriptive characteristics of the subjects are included in Table 4. All values were presented using mean, and standard deviation (SD).

Table 4 Subjects characteristics.

Characteristics	***Mean ± SD***
Age (yrs)	21 ± 2
Height (cm)	176 ± 6
Body mass (kg)	68 ± 8
Fat percentage (%)	10 ± 2
VO_2max ($ml.kg^{-1}.min^{-1}$)	56 ± 2
Training experience (yrs)	5 ± 1

N = 10.Values = mean ± SD. VO2max = predicted maximal oxygen consumption.

Interleukin- 6

Plasma Interleukin- 6 concentrations was measured as inflammatory marker. At the baseline, there was no significant difference for Interleukin- 6 between trials. Concentration of Plasma Interleukin- 6 in LGI group was less than HGI and placebo groups, Interleukin- 6 increased significantly after exercise in 3 groups (all $P < 0.05$), there was significant difference for plasma Interleukin- 6 concentration between placebo, and low glycemic groups in after exercise ($P < 0.05$) and 1hour after exercise ($P < 0.05$). There was a significant interaction between trial, and time ($P=0.001$) (Figure 6).

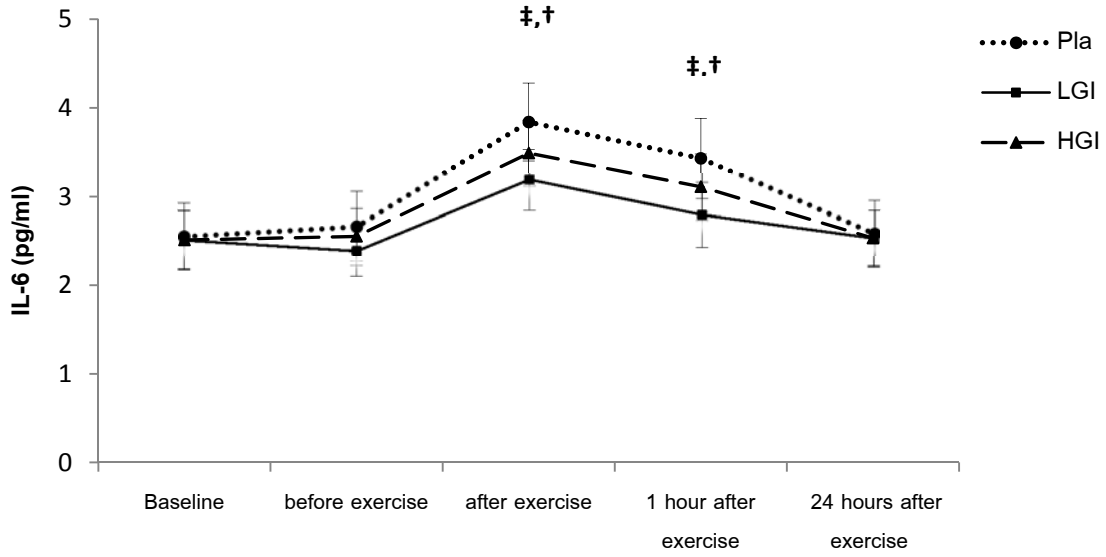

Figure 6 Mean concentration of plasma IL-6 for Pla, LGI, and HGI diet groups at the various time points. (‡); significant differences between Pla, and LGI ($P < 0.05$), (†); significant differences from baseline ($P < 0.05$), Pla; placebo, LGI; Low glycemic index, HGI; High glycemic index. Values are means ± SE.

Creatine Kinase

Creatine Kinase concentration was measured as a marker of muscle damage. At the baseline, there was no significant difference between trials. Concentration of serum Creatine Kinase in LGI group was less than HGI, and placebo groups. Creatine Kinasewas significantly elevated above baseline values at all- time points after exercise in 3 groups (all $P < 0.05$), but there was no significant difference in Creatine Kinase between 3 groups. There was no significant interaction between trial, and time (P=0.805) (Figure 7).

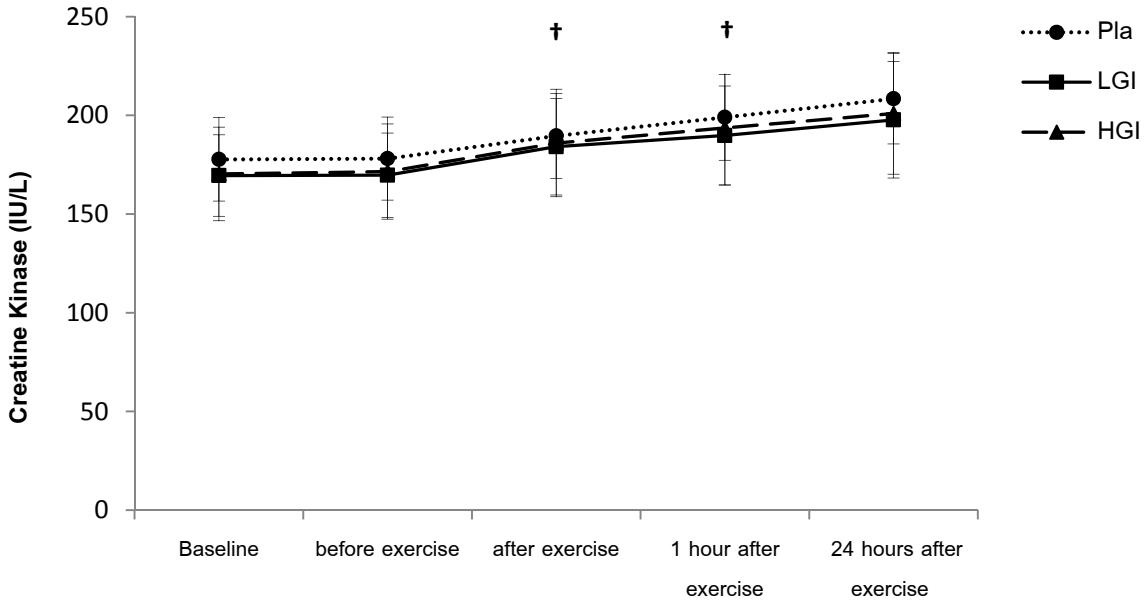

Figure 7 Means concentration of serum CK for Pla, LGI and HGI diet groups at the various time points. (†); significant differences from baseline ($P < 0.05$), Pla; placebo, LGI; Low glycemic index, HGI; High glycemic index. Values are means ± SE.

Blood glucose

At the baseline, there was no significant difference in glucose between trials. Concentration of glucose in HGI group was more than LGI and placebo groups, the serum concentration of glucose increased significantly above baseline values at before exercise, and decrease significantly after exercise in LGI, and HGI groups (all $P < 0.05$) . Furthermore there was significant difference in glucose between placebo with low glycemic groups ($P < 0.05$), and placebo, and high glycemic in before exercise ($P < 0.05$), also placebo with low glycemic groups ($P < 0.05$), and placebo with high glycemic in after exercise ($P = 0.01$). There was a significant interaction between trial, and time ($P=0.001$) (Figure 8).

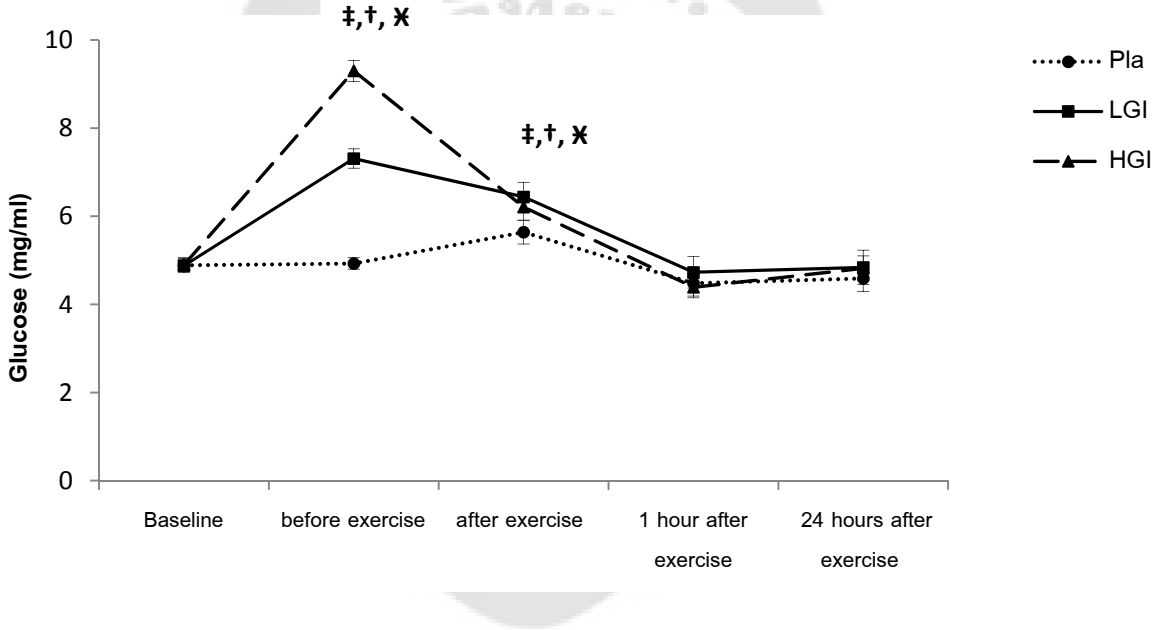

Figure 8 Mean concentration of serum glucose for Pla, LGI and HGI diet groups at the various time points. (‡); significant differences between Pla, and LGI ($P <0.05$), (✖); significant differences between Pla, and HGI ($P < 0.05$), (†); significant differences from baseline ($P < 0.05$). Pla; placebo, LGI; Low glycemic index, HGI; High glycemic index. Values are means ± SE.

Discussion

To our knowledge, this may be the first study that directly determined the role of GI as beverage on immune responses during endurance exercise. The major finding of the present study revealed that the consumption of a LGI beverage, before endurance exercise decreased the elevation of plasma IL-6 concentrations immediately after exercise, and during the 1 hour recovery period compared with the HGI, and placebo groups. These responses were accompanied by an attenuated increase in serum CK concentrations in LGI group compared with the HGI, and placebo groups at the end of the 1 hour recovery period. It has been reported that the noticeable increase in circulating IL-6 concentrations are related to exercise intensity, duration, mass of muscle involved, and endurance capacity (Bishop; et al. 2001: 490-503). In the present study, IL-6 increased immediately after exercise significantly. Recent studies demonstrate that IL-6 is produced by skeletal muscles contraction during exercise, and this release also related to contraction, and low muscle glycogen (Bishop; et al. 1999: 26-27). On the other hand, most studies of CHO intervention have used continuous prolonged exercise, duration, and CHO ingestion in this situation is effective in minimizing perturbations in circulating stress hormones, and immune responses (Bishop; et al. 2001: 490-503; Liu; et al. 2002: 492-498). CHO ingestion attenuated elevations in plasma IL-6 during both running, and cycling mainly because of its effect at the post-transcriptional level of IL-6 (Nieman. 1998: 64-76; Bishop; et al. 2001: 490-503; Pedersen; & Febbraio. 2008: 1379-1406; Nehlsen; et al. 1997: 1662-1667), whereas low muscle glycogen concentrations further enhanced IL-6mRNA, and the transcription rate for IL-6 (Steensberg; et al. 2003: 631-638). Therefore, muscle glycogen content appears to be an important stimulus for IL-6 which acts as an energy sensor. However, in our finding IL-6 in LGI group was significantly less than HGI, and placebo groups. In endurance exercise minimizing the glycemic response could sustain CHO supply during exercise, that cause to decrease the cortisol response, IL-6, and other inflammatory biomarkers (Bishop; et al. 2001: 490-503), however a HGI diet could increase pro-inflammatory cytokine (Kirwan; et al. 2001: 849-855). HGI diet is the exacerbation of glucose spike that occurs immediately after eating this spike could alter glucose and insulin dynamics during exercise (Pittas; et al. 2006: 2200-2209), which was in agreement with the findings in our present study.

Creatine kinase (CK) is an enzyme normally found only in skeletal muscle that used as an indirect marker of muscle damage in the present study. CK was measured during the time in three conditions, and increasing observed over the time. Concentration of serum CK in LGI group was less than HGI, and placebo groups but there were no significant changes in CK between three conditions. The phenomena of peak CK at 48 hours post-exercise as seen in the LGI group is also not uncommon (Malm; et al. 2004: 983-1000). This difference could be a result of a gradually increase in insulin following consumption of a LGI diet versus the HGI diet before exercise. Insulin is a powerful promoter of protein synthesis. On the other hand, CK can be elevated for several days in individuals (Miles; et al. 2010: 1456-1464) because of this our protocol couldn't have significant effect on CK concentration.

Conclusion

The consumption of the LGI beverage before exercise could minimize the increasing of plasma IL-6 concentration immediately after exercise, and during the 1 hour recovery period compared with the HGI beverage, and placebo. This acute improvement is consistent with studies that have noticed to the benefits of a LGI diet as most evident in individuals who follow this diet long-term. This result suggested that the LGI beverage consumed as pre-exercise meal could modify the inflammatory response in prolonged exercise. Further research is needed to establish the connection between glucose kinetics of GI meal and immune function, and also should look at the influence of muscle glycogen stores at the beginning of the study, as this could be an influencing factor in the metabolic variables. Moreover, plasma volume should be measured, and hematocrit and hemoglobin concentrations determined to ensure that changes in inflammatory molecules are indicative of inflammation, and not just a drop in plasma volume.

CHAPTER 4

Study 2: IL-6 responses to glycemic index during recovery from exercise.

Introduction

Inflammation is a generalized, systemic response, and can be triggered in a multitude of ways (Smith. 2000: 61-67). It is well accepted that eccentric exercise elicits an inflammatory response (Miles; et al., 2010). Macronutrient intake on the inflammatory process is of heightened interest, particularly effect of carbohydrate (CHO) consuming on inflammatory responses (Pedersen; & Febbraio. 2008: 1379-1406). One way to measure the effects of CHO in the body is through the use of the glycemic index (GI), which is a measure of the rate of glucose entry into the blood. Researchers have noted that when all other conditions were held constant, the only variable that was associated with improved insulin control was a low GI (LGI) diet as opposed to a high GI (HGI) diet (Solomon; et al. 2010: 1359-1368). The GI accounts for how rapidly glucose enters the blood based on CHO quality (Bishop; et al. 2001: 490-503). HGI diet is the exacerbation of glucose spike that occurs immediately after eating (Pittas; et al. 2006: 2200-2209).

Eccentric exercise is defined as the lengthening phase of muscle contraction, and investigators have established that it elicits greater inflammation than concentric or shortening contractions (Miles; et al. 2010: 1456-1464). While inflammatory cytokines increase immediately following exercise, they can remain elevated for up to four days following intense exercise (Smith. 2000: 61-67). Although CK is not directly related to muscular inflammation, it is a good marker of muscle damage, which in itself triggers an inflammatory response (Malm; et al. 2004: 983-1000). Feeding HGI carbohydrate immediately after exercise is useful for the restore of muscle glycogen, decreasing breakdown and increased repair of the muscle protein structure. HGI diet after exercise induces greater spike in insulin that cause to promote protein synthesis (Miles; et al. 2010: 1456-1464).

The purpose of this study was to determine whether there are differences in plasma interleukin- 6 concentrations, and glucose metabolism between low, and high GI during recovery from resistance exercise. Measured variables included interleukin-6 (IL-6), creatine kinase (CK), and glucose. It was hypothesized that all dependent variables would be lower in the HGI compared to LGI diet, and placebo groups after sub-max exercise. More

knowledge about inflammation, and glucose metabolism in exercise allow investigators to more effectively direct individuals towards proper diet for improving performance in athletes.

Methodology

Subjects

Ten males with more than 2 years of experience in regular strength training (2–3 times per week) volunteered to participate in the study. They were approved by the Tehran University Ethical Committee, and completed a medical history questionnaire to screen for contraindications that were excluded them from participation in the study, and subjects were excluded based on the following criteria: acute infections, recent oral surgery, injuries, and certain medications known to influence cytokine production such as non-steroidal anti-inflammatory medications or medical conditions, and if any medication had been taken during the 6 weeks prior to the study, and if symptoms of upper respiratory infection had been experienced in the 6 weeks prior to the study, and if symptoms of upper respiratory infection had been experienced in the 4 weeks prior to the study. Moreover, at the time of the study, all subjects were involved in normal training (2–3 times per week). Subjects were asked to refrain from alcohol consumption 24 hours prior to sample collection.

Research design

This study was a counterbalanced cross-over design, and the orders of the three trials were randomized, separated by at least 14 days. Subjects were instructed to keep their daily exercise to a minimum, and to standardize their diet during the 72 hours preceding each main trial. Each subject was kept 3 days diary of their dietary intake before the main trial. They were required repeating the same diet before each main trial to minimize the variation in muscle, and liver glycogen concentrations. Before each trial, they were reported to the laboratory after an overnight fast of 12 hours. This was to ensure an empty stomach, and to minimize the effect of a previous meal on the gastric emptying rate of the test meals.

Exercise familiarization

Subjects were come to the laboratory on four separate occasions. On the first visit, they were completed the medical history questionnaire, and have any questions answer prior to beginning any testing. Resting blood pressure, and pulse measurements were taken follow by anthropometric measurements of body mass, Body fat, and height. Following body composition screening, participants were completed a Maximal dynamic strength (1RM) for legs test using a 60° incline heavy duty legs press. After that subjects were familiarized with the resistance exercise protocol, in which they were required to resist the downward movement of the weights. This movement involves lengthening (eccentric) contractions of the knee extensor muscles. A hand winch (5:1 ratio; model number: F10217; line pull capacity: 700 kg; Jarrett Synergy, SA, Australia) was fit to the frame of the leg press, so that when the weight is lowered to the load-lowering point, the winch was used to lift the weight and reset it for the next repetition. In this model of lifting, the subjects only were completed lengthening muscle contractions, with no shortening (concentric) contractions.

On the day of the main trial, between four, and seven days after the first visit the subjects were brought to the laboratory at about 8:00 am after an overnight fast of 12 hours. After collection of the baseline blood samples the subjects were repeated the standardized warm-up on a stationary bicycle. The resistance exercise protocol consist of 5 sets of 10 lengthening contractions (5 sets, 10 repetitions in each set) at a workload of 120% 1RM) legs press. Each set was separated by a 2-mins rest interval. Subjects were instructed to lower the load in a controlled fashion to a 75° angle at the knee joint over 5 s (digital stopwatch, Cal. SO56, Seiko, Australia). During recovery from resistance exercise, subjects were consumed either the GI beverage : High-GI (GI = 83) glucose drink 15% weight per volume; 3 g/kg body mass GI = 83), Low-GI (GI = 36) fructose drink 15% weight per volume; 3 g/kg body mass GI = 36) or placebo (an equal volume of flavor- and color-matched artificially sweetened placebo)(Ross; et al. 2010: 5-12), in three time within 10 mins following exercise, and again at 50 and 110 mins. All of the trials were performed under similar conditions of barometric pressure, temperature, and relative humidity. No food was allowed until after the final blood sample was taken also their body mass were measured at the first of each trial.

Baseline measurements

Blood pressure: Blood pressure, and resting pulse measurements were taken using an Omron IntelliSense® Professional Blood Pressure Monitor (Model HEM-907XL, Health Check Systems, Inc., Brooklyn, NY) after participants sat quietly for ten minutes. **Body mass and body fat percentage:** Body mass was measured at the first of each trials by using a coin weight scale machine model fv1201 Japan. Excess clothing such as coats, sweatshirts, and shoes were removed, but no other clothing was removed, and body height was recorded using a stadiometer (seca® 240 wall-mounted), also the body fat percentage was measured using the caliper model 1127 Japan with 3 point Jackson Pollock (Jackson& Pollock, 1985) formula . The chest, abdomen and thigh sites were used to calculate the body fat percentage. The chest skin fold was a diagonal fold just in front of the armpit and in line with the nipple. The abdominal fold was a vertical fold approximately 1 inch to the right of the umbilicus and 1/2 inch below. The thigh fold was another vertical fold in the middle of the thigh, halfway between the hip crease, and the top of the kneecap.

1RM assessment

At least 1 week prior to commencing the study, in exercise familiarization session all subjects were reported to the laboratory to assess body mass, and legs strength. Maximal dynamic strength 1RM for legs was determined using a 60° incline heavy duty legs press. Following a 5-min warm up on a stationary bicycle, each subject was given 6 lifting attempts in order to achieve their 1RM. A valid repetition involve lowering the weight to the point of 75° of knee flexion (the load-lowering point) as measured by a Jarma goniometer (Therapeutic Equipment, Clifton, NJ), and then extending to full legs extension. Subjects were instructed to rest for 2–5 mins between repetitions to ensure a true maximal lift was achieved. After each successful lift, the load was increased by 2.5–5 kg until failure to complete one repetition. Subjects were given a maximum of 2 attempts to lift the weight; the greatest amount lifted successfully was recorded.

Lengthening contractions protocol

Subjects were repeated the standardized warm-up procedure (described previously). The resistance exercise protocol consisted of 5 sets with 10 repetitions lengthening contractions (at a workload of 120% 1RM) using legs (leg press). Each set was separated by a 2-mins rest interval. Subjects were instructed to lower the load in a controlled movement to a 75° angle at the knee joint over 5 sets (Digital stopwatch, Cal. SO56, Seiko, Australia).

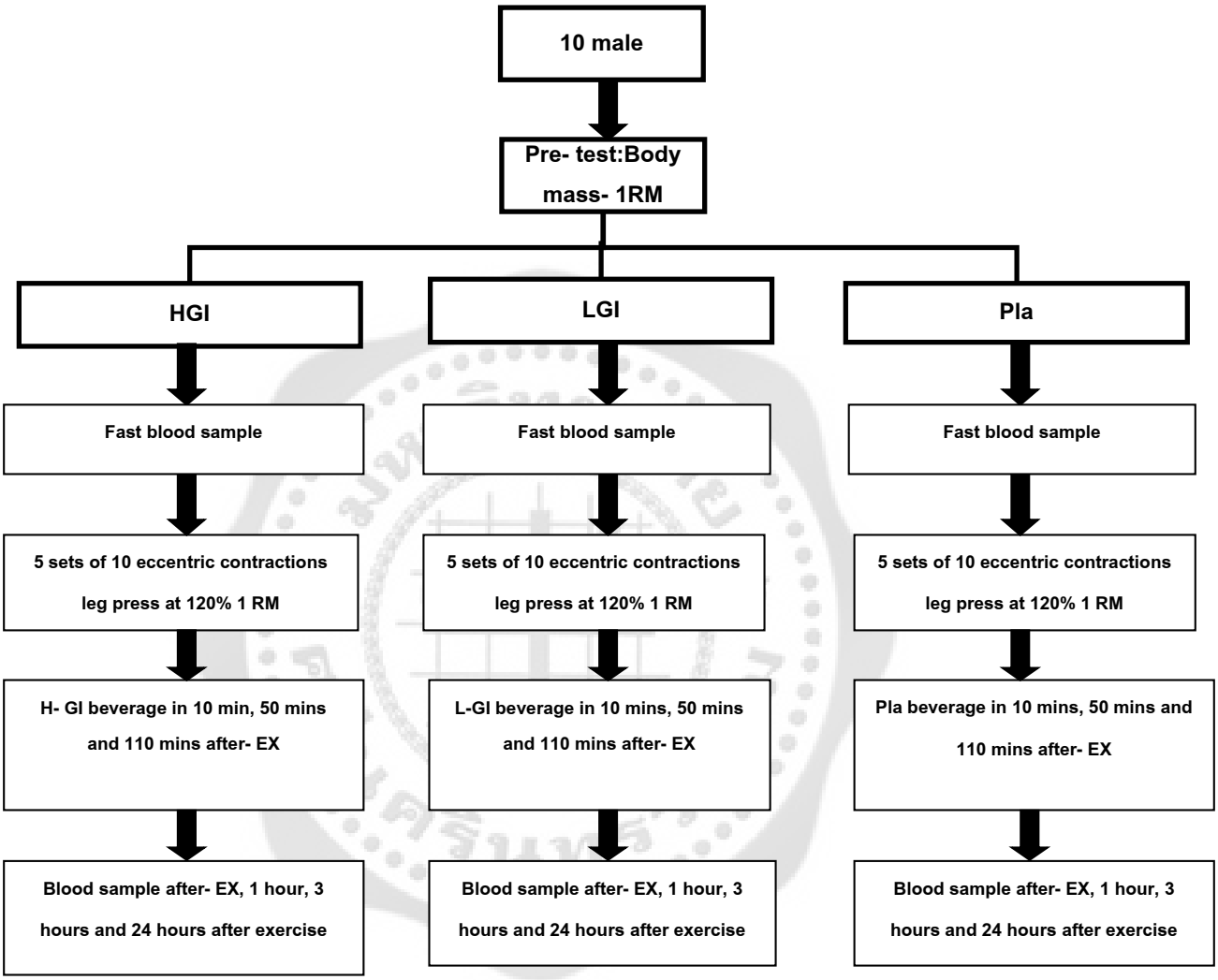

Figure 9 Represented chart of the experimental procedures, showing exercise bouts.

H-GI; glucose, 3 g/kg body mass (15%), L-GI; fructose 3 g/kg body mass (15%), Pla; placebo, EX: exercise.

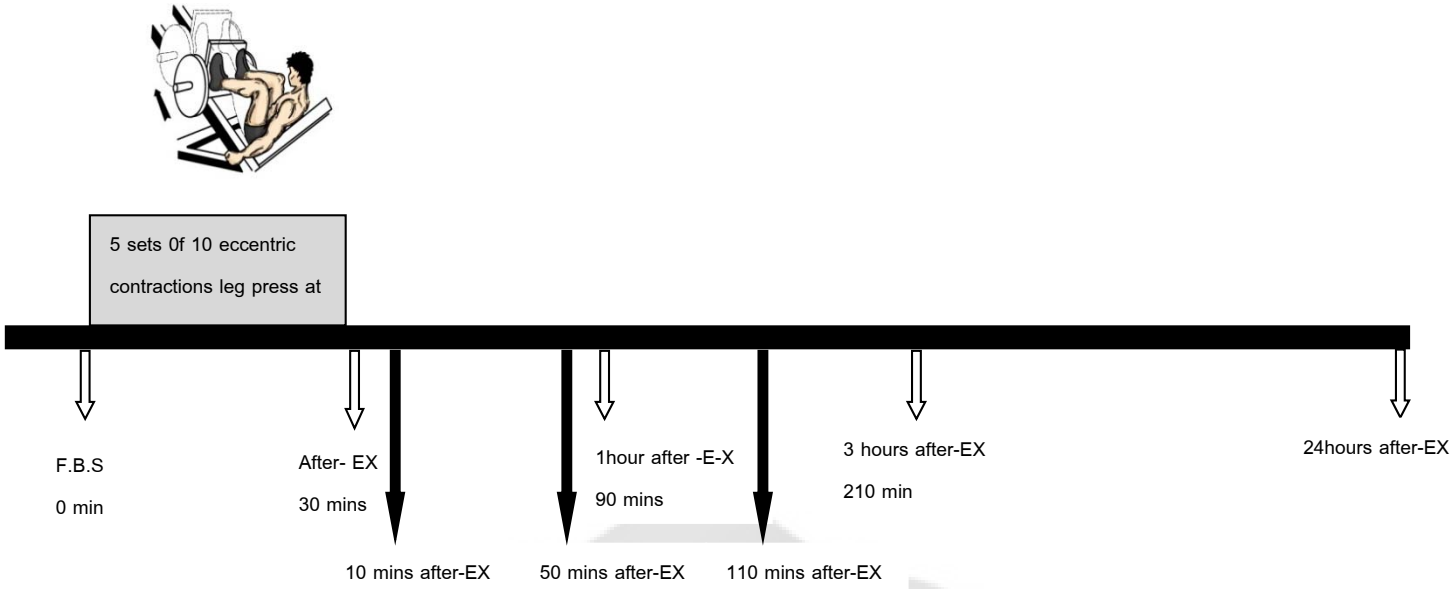

Figure 10 Schematic representations of the experimental procedures, showing an exercise bout.

: Consume beverage

: Blood sample taken for immune assessment

Blood analyses

10 ml venous blood was drawn from an antecubital vein in the forearm at each time point: 1- Fast blood sample (F.B.S), 2- Immediately post-exercise, 3 – 1 hour, 4 - 3 hours after exercise, 5- 24 hours after exercise during recovery period. Blood was drawn into a vacuum tube with clot activator, and serum separator for collection of serum to analyze glucose and CK. Plasma was separated immediately from blood cells by centrifugation at 2150 g at +4ºC for 15 mins, and was transferred into Eppendorf tubes, and immediately was frozen at −80°C until later analysis.

Plasma IL-6 was measured by high-sensitivity Enzyme-linked immunosorbent assay (ELISA) kit from R&D systems (Minneapolis, MN, USA). Its procedures were followed according to the kit specifications. Samples were diluted when necessary to ensure that the measurement fall within the range of the standard curve and creatine kinase (CK) was measured by the SYNCHRON® System(s) (Beckman Coulter, Inc.USA). Serum glucose was measured by BIOSEN C (EKF Diagnostic GmbH, West Germany) analyzer.

Statistical analyses

Samples size were calculated with a software that developed by Dr. David Schoenfeld with support from the MGH Mallinckrodt General Clinical Research Center. A total of 10 subjects were entered in this two-treatment crossover study. The probability is 84 percent that the study was detected a treatment difference at a two-sided 0.05 significance level, and difference between treatments is 1.500 units.

All collected data were presented as mean, and standard deviation (Mean ± SD). Before hypotheses tests, normality of data was checked out using Shapiro-wilk test as the number of observations. Box's M, and Levene's Tests were used to check out homogeneity of variances as well as equality of error variances between groups. As this study employed a repeated measure design, therefore, Mauchly's test was used to check sphericity assumption which refereed to the condition where the variances of the differences between all possible pairs of groups were equal, and then appropriate adjustments in the degrees of freedom were made. Repeated measures 5 (measurements: F.B.S , immediately post-exercise, 1 hour after exercise, 3 hours after exercise, and 24 hours after exercise) × 3 (groups: H-GI, L-GI and placebo) ANOVAs were applied to examine the main effects of independent variables (HGI, L-GI and placebo groups) on the IL-6, CK and glucose concentrations . Finally, significant within-group effects in all analyses were followed up by paired t- tests with an appropriate Bonferroni correction, and one-way ANOVAs and LSDs follow up tests were applied for significant between group effects. In all the above designs, H-GI, L-GI and placebo were considered as within-group, and between-group factors, respectively. Statistical significance was set at an alpha of $p < .05$. The data were analyzed using the statistical package SPSS, PC program, version 19.0 (SPSS Inc., USA).

Results

Ten healthy subjects participated in this study and completed 3 (H-GI, L-GI, and placebo) sessions of resistance exercise (consist of 5 sets of 10 lengthening contractions at a workload of 120% Maximal dynamic strength legs press). The descriptive characteristics of the subjects are included in Table 5. All values are presented using mean, and standard deviation (SD).

Table 5 Subjects characteristics.

Characteristics	***Mean ± SD***
Age (yrs)	22 ± 2
Height (cm)	177 ± 6
Body mass (kg)	83 ± 10
Fat percentage (%)	12 ± 2
Maximal dynamic strength (1RM) (kg)	235 ± 42
Training experience (yrs)	4 ± 1

N = 10. Values = mean ± SD.

Interleukin- 6

Plasma Interleukin- 6 concentrations was measured as inflammatory marker. At the baseline, there was no significant difference between trials. Concentration of plasma Interleukin- 6 in HGI group was less than LGI and placebo groups. Interleukin- 6 increased significantly after exercise in recovery time in 3 groups (all $P < 0.05$), except for 24 hours ($P < 0.05$), furthermore there was significant difference in Interleukin- 6 between placebo, and high glycemic groups in 3hours after exercise ($P < 0.05$). There was a significant interaction between trial, and time ($P=0.001$) (Figure 11).

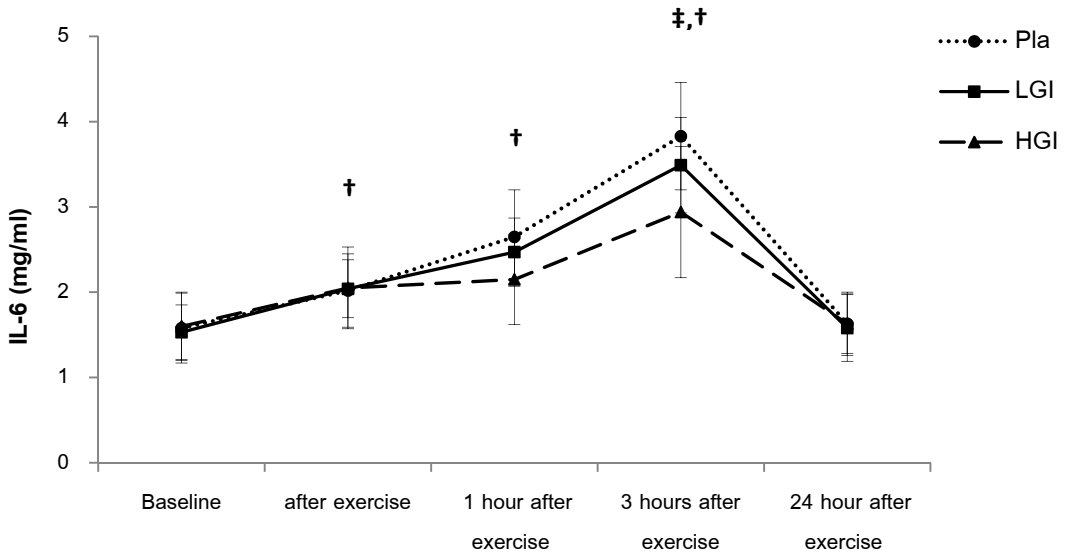

Figure 11 Means concentration of plasma IL-6 for Pla, LGI, and HGI diet groups at the various time points. (‡); significant differences between Pla, and HGI ($P < 0.05$), (†); significant differences from baseline ($P < 0.05$). Pla; placebo, LGI; Low glycemic index, HGI; High glycemic index. Values are means ±SE.

Creatine Kinase

Creatine Kinase concentration was measured as a marker of muscle damage. At the baseline, there was no significant difference for Creatine Kinase between trials. Concentration of serum Creatine Kinase in HGI group was less than LGI, and placebo groups, Creatine Kinase was significantly elevated above baseline values at all-time points during recovery in 3 groups (all $P < 0.05$), except for 1 hour after exercise in HGI group ($P < 0.05$), but there was no significant difference in Creatine Kinase between 3 groups. There was no significant interaction between trial, and time ($P=0.066$)

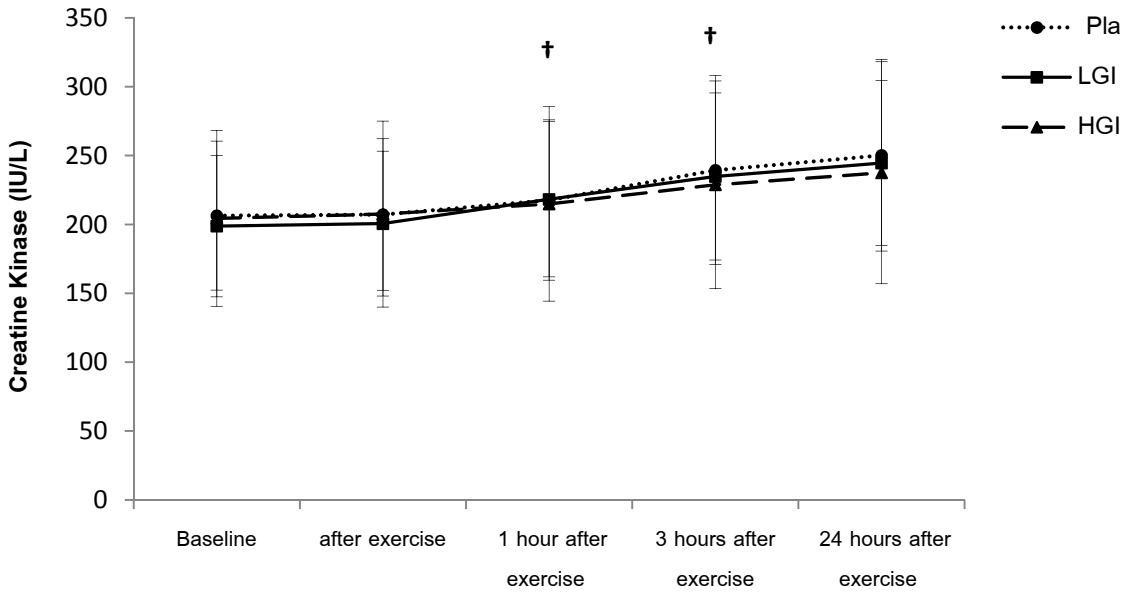

Figure 12 Means concentration of serum CK for Pla, LGI and HGI diet groups at the various time points. (†); significant differences from baseline ($P < 0.05$). Pla; placebo, LGI; Low glycemic index, HGI; High glycemic index. Values are means ± SE.

Blood glucose:

The serum concentration of glucose was measured to identify differences in the diets between conditions. At the baseline, there was no significant difference for glucose between trials. Glucose increased significantly following carbohydrate ingestion. Concentration of glucose in HGI group was more than LGI, and placebo groups, glucose was elevated above baseline values at 1hour after exercise in HGI and LGI groups (all $P < 0.05$). There was significant difference for glucose between placebo with low glycemic groups ($P=0.00$) and placebo with high glycemic ($P < 0.05$), also high glycemic with low glycemic groups ($P < 0.05$) in 1hour after exercise. Furthermore there was significant difference for glucose between placebo with high glycemic ($P < 0.05$), and also high glycemic with low glycemic group ($P < 0.05$) in 3hours after exercise. There was a significant interaction between trial, and time ($P=0.001$) (Figure 13).

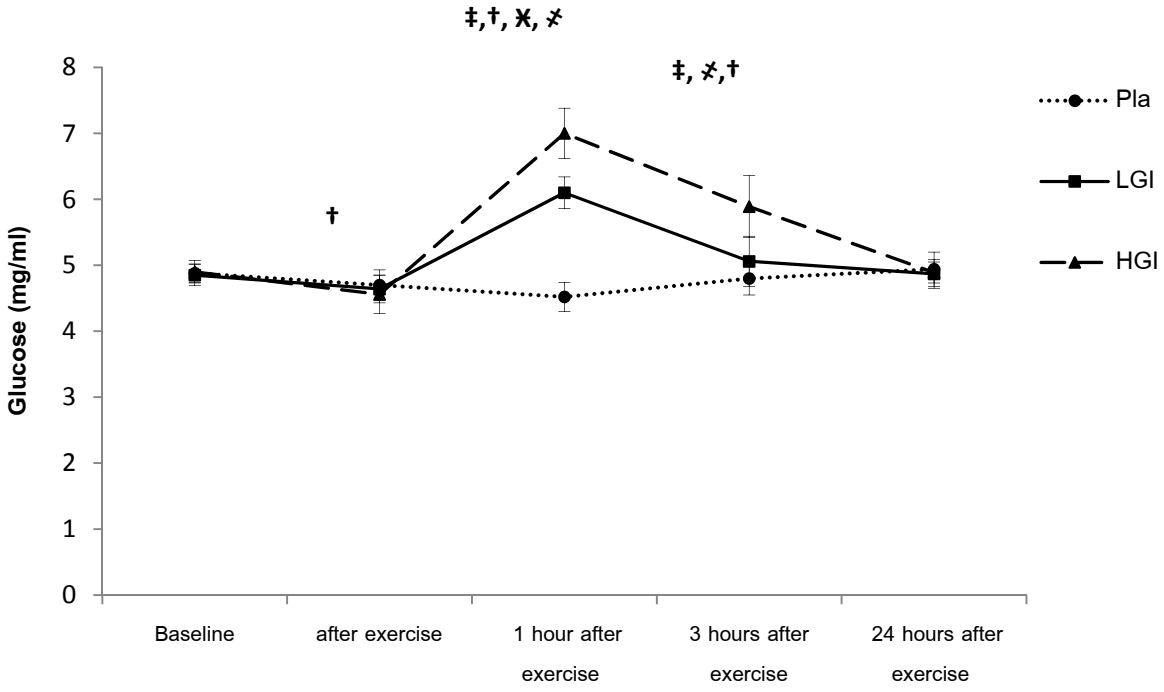

Figure 13 Means concentration of serum glucose for Pla, LGI, and HGI diet groups at the various time points. (✖); significant differences between Pla, and LGI ($P < 0.05$), (‡); significant differences between Pla, and HGI ($P < 0.05$), (≠); significant differences between LGI, and HGI ($P < 0.05$), (†); significant differences from baseline ($P > 0.05$). Pla; placebo, LGI; Low glycemic index, HGI; High glycemic index. Values are means ± SE.

Discussion

The aim of this study was to determine whether there are differences in plasma IL-6 concentration between low and high GI beverage during recovery from maximal lengthening contractions of the knee extensors. The key finding of the present study was that plasma IL-6 concentration decreased significantly in HGI group to compare with LGI and placebo groups at least during the early post-exercise recovery period. These reactions were jointed with an attenuated increase in serum CK concentrations in HGI group compared with the LGI and placebo groups at the end of the 3 hours recovery period.

We selected an exercise model that would induce moderate muscle damage with relatively little metabolic stress in skeletal muscle. Generally, eccentric exercise elicits an inflammatory response for repair and adaptation, leading to increases in IL-1 and IL-6 concentration, while anti-inflammatory cytokines appear to be down regulated, and inhibited (Peake; et al. 2005: 514-521). In current study, IL-6 significantly increased after exercise in three groups which was expected, as exercising skeletal muscle is a powerful stimulator of IL-6 (Petersen; & Pedersen. 2005: 1154-1162). No previous research has investigated cytokine responses during the early phase of recovery from eccentric contractions in different glycemic trials. The glycemic index is a scale that indicates how rapidly different foods influence blood glucose levels. The purpose of elevating blood glucose to the point of hyperglycemia in the high carbohydrate condition was because previous studies indicate that hyperglycemia can induce and or augment inflammation (Esposito; et al. 2002: 2067-2072; Gonzales et al., 1993: 224-231). The present data demonstrate that concentration of IL-6 in HGI group was significantly less than LGI, and placebo groups. Inflammation following muscle injury is important for tissue regeneration, but excess inflammation may delay tissue regeneration. The HGI diet could have resulted in a quicker glucose response, and therefore, a faster spike in insulin. HGI ingestion immediately following exercise is useful for the replenishment of muscle glycogen, resulting in limited breakdown, and increased repair of the muscle protein structure (Miles; et al. 2010: 1456-1464). HGI diet versus the LGI diet after exercise induces greater increase in insulin. Insulin is a powerful promoter of protein synthesis. Muscle injury combined with hyperglycemia attenuated plasma IL-6 concentrations (Stevenson; Williams; & Biscoe. 2005: 291-307).

Creatine kinase is indicative of loss of muscle integrity, and researchers have been suggested that muscle integrity is most compromised in high force eccentric contractions (Esposito; et al. 2002: 2067-2072). We also measured the serum concentrations of CK in recovery time after exercise; we observed that the serum concentrations of CK increased after exercise during recovery period. These findings complement data from other studies indicating that plasma/serum cytokine concentrations generally increase beyond 3 hours after resistance exercise (Smith. 2000: 61-67), and lengthening contractions of the leg muscles (MacIntyre; et al. 2001: 180-186), and arm muscles (Miles; et al. 2007: 507-520). According to our finding CK in HGI group was less than LGI, and Pla groups, but not significantly.

This increase in CK peaked at 24 hours post-exercise for the HGI group, which is consistent with previous research on downhill running (Esposito; et al. 2002: 2067-2072). CK can be elevated for several days in individuals (Miles; et al. 2010: 1456-1464). The exercise protocol in our study included only 50 single-leg contractions, whereas other studies have used upper, and lower body exercises (Smith. 2000: 61-67), and 200 single-leg contractions (MacIntyre; et al. 2001: 180-186). The smaller muscle mass, and lower number of contractions used during exercise may also account for the lack of any substantial systemic inflammatory response after exercise.

Conclusions

In summary, consuming HGI carbohydrate during recovery from exercise attenuate plasma IL-6 concentration. The results of this study present with several questions related to carbohydrate intake, inflammation and exercise. Much more research is required for a greater understanding of carbohydrate's role in inflammation. Future research could investigate the effects of consuming carbohydrate with different glycemic index, and load during recovery from other forms of exercise such as prolonged, and interval, which induces greater muscle injury, that require higher intake of carbohydrate to restore muscle glycogen content.

CHAPTER 5

GENERAL DISCUSSION

Discussion

The goal of this study was to gain a better understanding of the inflammatory process in skeletal muscle. It was hypothesized that there was difference in plasma IL-6 concentration, and glucose metabolism between low and high GI beverage in sub-max exercise, and also during recovery from resistance exercise. The major finding of the present study revealed that the consumption of a LGI beverage, before endurance exercise decreased the level of plasma IL-6 concentrations immediately after exercise, and during the 1 hour recovery period compared with the HGI, and placebo groups. These responses were accompanied by an attenuated increase in serum CK concentrations in LGI group compared with the HGI, and placebo groups at the end of the 1 hour recovery period. On the other hand, we found that plasma IL-6 concentration following resistance exercise decreased significantly in HGI group to compare with LGI, and placebo groups at least during the early post-exercise recovery period. These reactions were accompanied by an attenuated increase in serum CK concentrations in HGI group compared with the LGI, and placebo groups at the end of the 3 hours recovery period.

IL-6 is released from muscle during exercise due to increases in IL-6 transcription factors, mRNA levels and protein levels within the working muscle fibers (Bruunsgaard; et al. 2004: 237-241). This increase is associated with exercise related metabolic changes. Carbohydrate ingestion before, during and after exercise has been found to attenuate the response of IL-6 during an exercise session. The storage form of carbohydrate is glycogen, and also both longer duration and higher intensity exercise are known to deplete muscle glycogen stores more readily than exercise with short duration, and low intensity (Nieman; et al. 2003: 1283-1290). Within longer duration exercise studies, subjects tend to exhibit decreased muscle glycogen content, and hence an immediate post-exercise increase in IL-6 to increase glucose availability. One of the most important aspects of recovery that can be influenced by nutrition is the synthesis of muscle glycogen to replace stores lost during exercise. The amount, timing, and frequency of CHO ingestion have been shown to affect glycogen synthesis (Jentjens; & Jeukendrup. 2003: 117-144). The glycemic index is a scale

that indicates how rapidly different foods influence blood glucose levels. In endurance exercise minimizing the glycemic response could sustain CHO supply during exercise, that cause to decrease the cortisol response, IL-6, and other inflammatory biomarkers (Bishop; et al. 2001: 490-503). Consuming carbohydrate with HGI could have resulted in a quicker glucose response, and therefore, a faster spike in insulin. Consuming HGI carbohydrate immediately after exercise is useful for the replenishment of muscle glycogen, resulting in limited breakdown, and increased repair of the muscle protein structure (Miles; et al. 2010: 1456-1464). HGI diet versus the LGI diet after exercise induces greater spike in insulin that cause to promote protein synthesis (Miles; et al. 2007: 507-520). Muscle injury combined with hyperglycemia attenuated plasma IL-6 concentrations (Stevenson; Williams; & Biscoe. 2005: 291-307).

Conclusion

In summary in endurance exercise consuming a low glycemic CHO before exercise can have a beneficially effect on immune function by maintaining blood glucose in stable level, leading to lower stress hormone response, and IL production, which attenuates the inflammatory response in body during exercise. On the other hand, in resistance exercise consuming HGI carbohydrate during recovery from exercise attenuates plasma IL-6 concentration.

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APPENDEX A

APPENDEX A

Personal Medical History Survey

Complete the front and back of this form.

Name: Date:

Address: City/State: Zip:

Phone: E-mail Adress:

Age: Sex: Weight: Height:

1. Have you ever been diagnosed as having: (check all that apply)

	Never	Past	Presently
A. Heart disease _____			
B. Rheumatic fever			
C. High blood pressure			
D. Other vascular disorders			
E. Diabetes			
F. Kidney disease			
G. Asthma			
H. Allergies			
I. Chronic bronchitis			
J. Other respiratory illness			
K. High serum lipids (cholesterol)			
L. Anemia			
M. Low blood sugar			
N. Neuro-musculo-skeletal disease			
O. Sores in mouth			
P. Cavities in teeth			
Q. Gum disease			

R. “Strep” throat

S. Other oral infections

2. Please indicate any surgery that you have undergone and the approximate date(s).

3. Please indicate recent illnesses or major injuries that you have had. Also list approximate dates.

_____

4. Do you smoke? Packs per day?

Do you use smokeless tobacco (chew or dip)? How often?

5. Please list all medications or supplements (prescription and non-prescription) that you are presently taking.

Duration	Medication	Dosage

6. Describe exercise or activity program during the last 2 months (excluding your taper). (Please include: the activity, amount per day, days per week, and length of time you have been exercising at this level)

Activity minutes/day days/week

weeks of exercise _____

7. How long was your taper? _____ days

8. How many long course distance races have you completed in the past? _____

9. When did you start training for this triathlon?_____

10. Have you smoked any tobacco product in the last 2 hours? No Yes

When?

11. Used any smokeless tobacco product in the last 2 hours? No Yes

When?

12. Have you chewed gum in the last 2 hours? No Yes

When?

13. When did you last eat? (Meal or snack; anything)

14. When did you last brush your teeth? _____

15. Have you exercised today? If so, what did you do?

Signature Date

APPENDEX B

APPENDEX B

OUTPUT FROM THE STATISTICAL ANALYSES

Study 1: Interleukin- 6

Table 1. Descriptive statistics.

Groups	Time				
	Baseline	before exercise	after exercise	1hour after exercise	24 hours after exercise
Placebo	2.5630(0.37)	2.6730(0.39)	3.8450(0.44)	3.4340(0.45)	2.5990(0.37)
Low glycemic	2.5290(0.33)	2.4060(0.29)	3.1980(0.34)	2.8030(0.36)	2.5450(0.31)
High glycemic	2.5110(0.33)	2.5540(0.32)	3.4920(0.37)	3.1150(0.37)	2.5390(0.32)

Table 2. ANOVA Test.

IL-6		Sum of Squares	df	Mean Square	F	Sig.
Baseline	Between Groups	.014	2	.007	0.05	0.94
	Within Groups	3.272	27	.121		
	Total	3.286	29			
Before exercise	Between Groups	.358	2	.179	1.05	0.23
	Within Groups	3.148	27	.117		
	Total	3.506	29			
After exercise	Between Groups	2.099	2	1.049	6.92	0.004
	Within Groups	4.090	27	.151		
	Total	6.189	29			
1hour after exercise	Between Groups	1.991	2	.995	6.17	0.006
	Within Groups	4.351	27	.161		
	Total	6.342	29			
24 hours after exercise	Between Groups	.022	2	.011	0.09	0.91
	Within Groups	3.162	27	.117		
	Total	3.184	29			

Table 3. Multiple Comparisons (Test Bonferroni)

After exercise	Mean Difference (I-J)	sig
Placebo		
Low glycemic	.64700*	.003
High glycemic	.35300	.158
Low glycemic		
placebo	-.64700*	.003
High glycemic	-.29400	.308
High glycemic		
placebo	-.35300	.158
low glycemic	.29400	.308

Table 4. Multiple Comparisons (Test Bonferroni)

1hours	Mean Difference (I-J)	sig
Placebo		
Low glycemic	.63100*	.005
High glycemic	.31900	.261
Low glycemic		
placebo	-.63100*	.005
High glycemic	-.31200	.281
High glycemic		
placebo	-.31900	.261
low glycemic	.31200	.281

Creatine Kinase

Table 5. Descriptive statistics.

Groups	Time				
	Baseline	Before exercise	after exercise	1hour after exercise	24 hours after exercise
Placebo	177.7(21.17)	178.1(21.01)	189.6(21.52)	199(21.72)	208.4(22.86)
Low glycemic	169.5(20.65)	169.7(21.36)	184.1(24.47)	189.8(25.08)	197.7(29.49)
High glycemic	170.3(23.7)	171.5(24.12)	186(27.23)	193.7(29)	201(30.81)

Table 6. ANOVA Test.

		Sum of Squares	Df	Mean Square	F	Sig.
Baseline	Between Groups	408.800	2	204.400	0.42	0.65
	Within Groups	12944.700	27	479.433		
	Total	13353.500	29			
Before exercise	Between Groups	391.200	2	195.600	0.39	0.67
	Within Groups	13313.500	27	493.093		
	Total	13704.700	29			
After exercise	Between Groups	156.067	2	78.033	0.13	0.87
	Within Groups	16229.300	27	601.085		
	Total	16385.367	29			
1hour after exercise	Between Groups	426.467	2	213.233	0.329	0.72
	Within Groups	17473.700	27	647.174		
	Total	17900.167	29			
24 hours after exercise	Between Groups	600.467	2	300.233	0.38	0.68
	Within Group	21072.500	27	780.463		
	Total	21672.967	29			

Glucose

Table 7. Descriptive statistics.

Groups	Time				
	Baseline	before exercise	after exercise	1hour after exercise	24 hours after exercise
Placebo	4.89(0.12)	4.93(0.13)	5.64(0.27)	4.48(0.33)	4.59(0.30)
Low glycemic	4.88(0.16)	7.31(0.22)	6.44(0.33)	4.73(0.36)	4.84(0.39)
High glycemic	4.90(0.16)	9.30(0.24)	6.21(0.30)	4.39(0.20)	4.82(0.28)

Table 8. ANOVA Test.

glucose		Sum of Squares	df	Mean Square	F	Sig.
Baseline	Between Groups	.003	2	.001	0.05	0.95
	Within Groups	.614	27	.023		
	Total	.617	29			
Before exercise	Between Groups	95.481	2	47.741	1112.8	0.00
	Within Groups	1.148	27	.043		
	Total	96.629	29			
After exercise	Between Groups	3.397	2	1.699	18.35	0.000
	Within Groups	2.498	27	.093		
	Total	5.896	29			
1hour after exercise	Between Groups	.625	2	.312	3.26	0.05
	Within Groups	2.586	27	.096		
	Total	3.211	29			
24 hour after exercise	Between Groups	.403	2	.201	1.85	0.17
	Within Groups	2.934	27	.109		
	Total	3.337	29			

Table 9. Multiple Comparisons (Test Bonferroni).

Before exercise	Mean Difference (I-J)	sig
Placebo		
Low glycemic	-2.37900*	.000
High glycemic	-4.36400*	.000
Low glycemic		
placebo	2.37900*	.000
High glycemic	-1.98500*	.000
High glycemic		
placebo	4.36400*	.000
low glycemic	1.98500*	.001

Table 10. Multiple Comparisons (Test Bonferroni).

After exercise	Mean Difference (I-J)	sig
Placebo		
Low glycemic	-.79900*	.000
High glycemic	-.57500*	.001
Low glycemic		
placebo	.79900*	.000
High glycemic	.22400	.334
High glycemic		
placebo	.57500*	.001
low glycemic	-.22400	.334

STUDY 2

Interleukin- 6

Table 11. Descriptive statistics.

Groups	Time				
	Baseline	after exercise	1hour after exercise	3hours after exercise	24 hours after exercise
Placebo	1.58(0.41)	2.02(0.43)	2.65(0.55)	3.83(0.63)	1.63(0.35)
Low glycemic	1.53(0.32)	2.04(0.34)	2.47(0.40)	3.49(0.56)	1.58(0.39)
High glycemic	1.60(0.40)	2.05(0.48)	2.15(0.53)	2.94(0.77)	1.63(0.37)

Table 12. ANOVA Test.

IL-6		Sum of Squares	df	Mean Square	F	Sig.
Baseline	Between Groups	.021	2	.011	0.07	0.93
	Within Groups	3.957	27	.147		
	Total	3.979	29			
after exercise	Between Groups	.006	2	.003	0.01	0.98
	Within Groups	4.807	27	.178		
	Total	4.812	29			
1hour after exercise	Between Groups	1.295	2	.648	2.55	0.09
	Within Groups	6.837	27	.253		
	Total	8.132	29			
3hours after exercise	Between Groups	4.089	2	2.044	4.6	0.01
	Within Groups	11.788	27	.437		
	Total	15.876	29			

24 hours after exercise	Between Groups Within Groups Total	.015 3.831 3.845	2 27 29	.007 .142	0.05	0.91

Table 13. Multiple Comparisons (Test Bonferroni)

3hours	Mean Difference (I-J)	sig
Placebo		
Low glycemic	.34200	.772
High glycemic	.89600*	.016
Low glycemic		
placebo	-.34200	.772
High glycemic	.55400	.215
High glycemic		
placebo	-.89600*	.016
low glycemic	-.55400	.215

Creatine Kinase

Table 14. Descriptive statistics.

Groups	Time				
	Baseline	after exercise	1hour after exercise	3hours after exercise	24 hours after exercise
Placebo	206.4(54.09)	207.2(55.04)	217.7(58.19)	239.4(68.65)	250.2(69.49)
Low glycemic	198.8(63.83)	200.6(67.50)	218.3(70.61)	234.8(75.31)	244.6(80.56)
High glycemic	204.4(51.36)	207.5(52.59)	214.9(56.34)	228.8(60.65)	237.5(59.80)

Table 15. ANOVA Test.

		Sum of Squares	Df	Mean Square	F	Sig.
Baseline	Between Groups	310.400	2	155.200	0.04	0.95
	Within Groups	86754.400	27	3213.126		
	Total	87064.800	29			
after exercise	Between Groups	304.200	2	152.100	0.04	0.95
	Within Groups	92892.500	27	3440.463		
	Total	93196.700	29			
1hour after exercise	Between Groups	65.867	2	32.933	0.009	0.99
	Within Groups	103931.100	27	3849.300		
	Total	103996.967	29			
3hours after exercise	Between Groups	565.067	2	282.533	0.06	0.94
	Within Groups	126585.600	27	4688.356		
	Total	127150.667	29			
24 hours after exercise	Between Groups	810.200	2	405.100	0.08	0.92
	Within Groups	134060.500	27	4965.204		
	Total	134870.700	29			

Glucose

Table 16. Descriptive statistics.

Groups	Time				
	Baseline	after exercise	1hour after exercise	3hours after exercise	24 hours after exercise
Placebo	4.88(0.14)	4.70(0.23)	4.52(0.22)	4.80(0.25)	4.94(0.26)

Low glycemic	4.85(0.16)	4.64(0.21)	6.10(0.24)	5.06(0.38)	4.87(0.22)
High glycemic	4.90(0.17)	4.56(0.29)	7.00(0.38)	5.89(0.47)	4.89(0.16)

Table 17. ANOVA Test.

glucose		Sum of Squares	df	Mean Square	F	Sig.
Baseline	Between Groups	.017	2	.008	0.30	0.73
	Within Groups	.731	27	.027		
	Total	.748	29			
after exercise	Between Groups	.092	2	.046	0.73	0.48
	Within Groups	1.681	27	.062		
	Total	1.773	29			
1hour after exercise	Between Groups	31.654	2	15.827	181.89	0.00
	Within Groups	2.349	27	.087		
	Total	34.003	29			
3hours after exercise	Between Groups	6.506	2	3.253	22.24	0.00
	Within Groups	3.948	27	.146		
	Total	10.454	29			
24 hours after exercise	Between Groups	.032	2	.016	0.317	0.73
	Within Groups	1.349	27	.050		
	Total	1.381	29			

Table 18. Multiple Comparisons (Test Bonferroni).

1hours	Mean Difference (I-J)	sig
Placebo		
Low glycemic	-1.58400*	.000
High-glycemic	-2.48500*	.000
Low glycemic		
placebo	1.58400*	.000

High glycemic	-.90100*	.000
High glycemic		
placebo	2.48500*	.000
low glycemic	.90100*	.000

Table 19. Multiple Comparisons (Test Bonferroni).

3 hours after exercise	Mean Difference (I-J)	sig
Placebo		
Low glycemic	-.25700	.433
High glycemic	-1.09100*	.000
Low glycemic		
placebo	.25700	.433
High glycemic	-.83400*	.000
High glycemic		
placebo	1.09100*	.000
low glycemic	.83400*	.000

VITAE

VITAE

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Educational Background:

2005	Training of Physical Training teacher and Sport Sciences (B.Sc.) Qom University
2009	Physical Training and Sport Sciences (M.Sc.) Islamic Azad University
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