DOES MODERATE INTENSITY EXERCISE IN THE POSTPRANDIAL PERIOD
ATTENUATE THE INFLAMMATORY RESPONSE TO A HIGH-FAT MEAL?

by

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Abstract

Background: High-fat meals (HFM) have been shown to increase postprandial lipemia (PPL) and inflammation. Acute exercise both pre and post-meal has been shown to attenuate PPL and inflammation. However, studies examining the interaction of HFMs and exercise on PPL and inflammation have used meal and exercise conditions more extreme than typical for average adults. The purpose of this study was to determine if moderate intensity exercise following a "true-to-life" HFM would attenuate PPL and inflammation.

Methods: Participants were thirty-nine young adults (18-40 years) with no known metabolic disease. Inclusion criteria consisted of participants meeting physical activity guidelines of ≥ 150 min/week of moderate-to-vigorous physical activity or ≥ 75 min/week of vigorous activity, or <30 min of planned physical activity per week. Participants were block randomized to EX or CON groups. Participants consumed a HFM of 10 kcal/kgbw. The EX group walked at 60% VO_{2peak} to expend ≈ 5 kcal/kgbw beginning one-hour following the HFM. The CON group remained sedentary during the postprandial period. Blood samples were collected at baseline and 2, and 4hrs postprandially.

Results: At baseline, there were no differences between EX and CON groups for any metabolic or inflammatory markers ($p>0.05$). Postprandial TRG increased $\approx 100\%$ ($p<0.001$) in both groups, with no differences between groups. HDL concentrations decreased across time in both groups ($p<0.001$) with no differences between groups ($p=0.338$). HDL was higher in the EX group at 2hrs ($p=0.047$), but not 4hrs ($p=0.135$). IL-6 and TNF-α concentrations did not change over time with no differences between groups ($p>0.05$). The EX group increased sVCAM-1 from baseline to 4hr ($p=0.003$), while the CON group did not. Change in TRG was associated with change IL-6, IL-8, IL-10 and TNF-α from baseline to 2hrs when controlling for VO_{2peak} and body fat%. No other associations were seen between change scores for TRG and inflammatory markers.

Conclusions: Despite significant increases in PPL following a HFM, moderate intensity exercise in the postprandial period did not mitigate the PPL nor the inflammatory response to the HFM. These results indicate PPL and inflammation following a HFM are not directly related in a young, healthy population with low metabolic risk.

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Dedication

I would like to dedicate this thesis to my parents Johnny and Teresa Teeman. Our entire family has gone through big changes over the last two years, but your support for me has been unwavering. It is to you both that I owe the aptitude to make difficult decisions, the confidence to pursue my own dreams, and the humility to appreciate all who have helped me along the way.

Chapter 1 - Literature Review

Introduction

A typical Western diet contains highly calorically dense and nutrient poor foods; including large portions of meat, refined grains, and pre-packaged foods (Popkin, 2011). As Western diets have become more common in developed countries around the world, atherosclerotic related deaths have also increased (Dahlof, 2010). The average fat content of a Western meal is between 20 and 40 grams of fat, and three to four meals per day are consumed regularly (Sharrett et al., 2001); therefore a typical individual spends the majority of their waking day in the postprandial (post-meal) state. Extensive research over the last several decades has focused on one of the main components of the Western diet, the high-fat content, and its role in the development of atherosclerosis.

Throughout much of the 20th century, atherosclerosis was thought to be merely a disease of excess lipids in the bloodstream. However, recent evidence has shown the progression of the disease to be more related to inflammation within the blood vessel wall (Libby, 2012). Accordingly, individuals with high levels of systemic inflammation have an increased risk for sudden cardiac events and mortality (Okazaki et al., 2014; Ridker, Buring, Shih, Matias, & Hennekens, 1998; Su et al., 2013). Researchers have studied the relationship between dietary fat and circulating inflammatory markers exploring a link between a single high-fat meal and postprandial inflammation (Lundman et al., 2007; Nappo et al., 2002) as well as endothelial dysfunction (Vogel, Corretti, & Plotnick, 1997). The postprandial inflammatory response is related, in part, to a prolonged elevation of triglycerides in the blood stream known as postprandial lipemia or (PPL). Prolonged elevated triglycerides allow for high density

lipoproteins (HDL) to be cleared from the blood stream easily, and for small, atherogenic low density lipoproteins (LDL) particles to form (Chapman, Le Goff, Guerin, & Kontush, 2010).

Evidence suggests an association between PPL and inflammation, and this association has helped focus research around exercise and aerobic training as possible modalities to help attenuate PPL (Tsetsonis & Hardman, 1996a; Merrill et al., 1989). More physically active individuals tend to have lower levels of systemic inflammation than less active individuals (Kasapis & Thompson, 2005). This relationship has been observed in youth (Harmse & Kruger, 2010), elderly (Jankford & Jemiolo, 2004), and athletic (Tomaszewski et al., 2003) populations. A possible mechanism for this attenuated inflammation may be lower postprandial triglyceride concentrations. Individuals with greater aerobic fitness have an increased ability to clear lipids from their blood stream postprandially (Cohen, Noakes, & Benade, 1989; Merrill et al., 1989). However, the benefits of exercise training for postprandial lipemia appear to be relatively short lived. Only a few days with no exercise may completely negate any attenuation of PPL from the last bout of exercise (Hardman, Lawrence, & Herd, 1998). Due to the short-term nature of the effects of acute exercise on PPL, researchers have examined a variety of factors including: exercise timing, type, and intensity, in an attempt to maximize the lipid lowering effects of exercise. The majority of these studies have examined triglyceride clearance from circulation; however, fewer studies have provided insight into the relationship between acute exercise and postprandial inflammation after a high-fat meal.

In this literature review we will consider the postprandial inflammatory response to high-fat, high-calorie, Western meals and the potential role of exercise as a modality of attenuating PPL and inflammation. A brief review of potential mechanisms whereby high-fat meals may exert inflammatory and atherosclerotic promoting actions will also be included.

Postprandial Hyperlipidemia

Due in part to the modernization of the food industry in many developed countries around the world, a typical individual spends the majority of their day in a postprandial state (Sharrett et al., 2001). The magnitude of the postprandial lipid increase is directly proportional to the fat content of the meal up to approximately 80 grams (Lopez-Miranda, Williams, & Lairon, 2007). Many metabolic processes determine the overall magnitude and duration of PPL. Recently digested lipids must be absorbed and secreted in the form of chylomicrons from the intestine, and very low density lipoproteins (VLDL) are secreted from the liver. Chylomicrons and VLDLs are jointly known as triglyceride rich lipoproteins (TRL) in circulation.

Plasma triglyceride concentrations in the postprandial state are an independent factor of coronary heart disease (Patsch, Karlin, Scott, Smith, & Gotto, 1992). The mechanisms of TRLs causing damage to the vascular wall are not fully understood; however, several proposed mechanisms may explain the increased cardiovascular risk associated with elevated postprandial TRLs. Increased TRLs in circulation lead to a greater transfer of triglyceride from TRLs to cholesterol rich lipoproteins (mainly HDL) via cholesterol ester transfer protein (Chapman et al., 2010). The prolonged elevation of TRLs after a high fat meal enhances the lipid exchange between these particles. This process both depletes HDL cholesterol concentrations (Lamarche et al., 1999) and increases concentrations of small, dense, LDL and chylomicron (CM) remnants (Williams & Tabas, 1995). These small, dense lipoprotein remnants appear to have less LDL-receptor binding affinity (Galeano et al., 1994), allowing them to stay in circulation longer and become atherogenic through their ability to penetrate the vascular endothelium (Griffin, 1999).

Postprandial Inflammatory Response

Once the small, dense CM and LDL particles are inside the endothelium they are oxidized by reactive oxygen species (Witztum & Steinberg, 1991). Monocytes are recruited to the endothelial surface by increased expression of vascular adhesion molecule-1 (VCAM-1) (Huo, Hafezi-Moghadam, & Ley, 2000). VCAM-1 expression may be increased via oxidized LDL particles that may activate the NF-kβ pathway (Kawakami et al., 2006). The NF-kβ pathway may be activated by the endothelium due to the TLR-2 receptor for Apo-CIII on VLDL (Kawakami et al., 2006). Monocytes penetrate the endothelial wall and become macrophages as they scavenge oxidized LDL and CMs and engulf these lipid rich particles. As these macrophages accumulate lipid they become foam cells. As foam cells increase in number they form a fatty streak (Agel, Ball, Waldmann, & Mitchinson, 1985). This process is the initiation of an atherosclerotic plaque.

There are a variety of cytokines secreted from macrophages that contribute to the progression of atherosclerosis. Many of these cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor- alpha (TNF-α), leads to the production of downstream cytokines and various other inflammatory markers that play vital roles in the regulation of atherosclerotic plaques. Although there are dozens of biomarkers associated with the initiation and development of atherosclerosis, we have chosen to focus on a few that are frequently implicated atherosclerotic development.

One of the most commonly researched markers of postprandial inflammation is IL-6. IL-6 is secreted from endothelial cells, T cells and macrophages within the vascular endothelium, as well as from adipose tissue (Abeywardena, Leifert, Warnes, Varghese, & Head, 2009). In the context of the postprandial period, IL-6 is generally considered to be pro-inflammatory. Its role as a pro-inflammatory cytokine has largely been documented from studies showing increased

levels of IL-6 correlating with greater occurrence of cardiac events (Harris et al., 1999). More recently it has been considered a myokine, because of its secretion from skeletal muscle tissue during exercise (Petersen & Pedersen, 2004). Its role as a myokine is generally considered to be anti-inflammatory and will be discussed in detail later. IL-6 also has important roles in the synthesis of C-Reactive Protein (CRP) (Casas, Shah, Hingorani, Danesh, & Pepys, 2008) and regulation of TNF-α (Schindler, 1990). IL-6 has consistently been shown to increase during the postprandial period following high-fat, high calorie meals (Payette et al., 2009; Poppitt et al., 2008; Miglio et al., 2013).

TNF-α is another marker of systemic inflammation that is often measured postprandially. TNF-α is produced by macrophages, endothelial cells (Beautler & Cerami, 1989), and adipose tissue (Kern et al., 1995). TNF-α has been shown to induce the expression of leukocyte cellular adhesion molecules such as VCAM-1 and intracellular adhesion molecule-1 (ICAM-1) (Meager, 1999). Additionally, TNF-α may also enhance the production of other cytokines and stimulate the production of growth factors (Libby et al., 1986). TNF-α responses in the postprandial period have been mixed. In subjects with metabolic syndrome and healthy-aged matched controls TNF-α has been shown to increase postprandially (Esposito et al., 2007). However, other studies have reported no change (Poppitt et al., 2008) or even a small decrease (Payette et al., 2009) in TNF-α postprandially. These conflicting results are most likely due to differences in subject characteristics between studies. TNF-α concentrations may be increased in subjects with greater abdominal adiposity and/or advanced age.

Interleukin-1β (IL-1β) is a member of the IL-1 family that has been implicated in nearly all aspects of the atherosclerotic process. IL-1β may be present in monocytes and macrophages (Unlu et al., 2007) as well as adipose tissue (Rocha & Libby, 2008). When secreted, IL-1β may

lead to the downstream production of other inflammatory markers such as IL-6 and CRP (Dinarello, 1996). IL-1β has been shown to promote an atherogenic lipid profile through the increased production and decreased clearance of VLDLs (Khovidhunkit et al., 2004). This results in hypertriglyceridemia and a pro-atherogenic environment. Additionally, the pro-inflammatory environment caused my IL-1β may promote structural changes in LDL particles that results in the smaller, denser, atherosclerotic LDLs that can be easily oxidized (Chait, Brazg, Tribble, & Krauss, 1993; Steinberg, Parthasarathy, Carew, Khoo, & Witztum, 1989). Further IL-1β may be secreted from macrophages when they engulf these oxidized LDLs that would continue stimulation of the inflammatory/pro-atherogenic environment. IL-1β may also directly initiate the development of atherosclerotic plaques through the recruitment of cellular adhesion molecules which facilitate the migration of many inflammatory cells to the vascular endothelium (Apostolakis, Vogiatzi, Krambovitis, & Spandidos, 2008). IL-1β does not appear to increase after a high-fat meal in healthy subjects (Fogarty et al., 2014; Cheng et al., 2010), but may in individuals with metabolic syndrome (Devaraj, Wang-Polagruto, Polagruto, Kenn, & Jialal, 2008).

Interleukin-8 (IL-8) is a cytokine commonly found in atherosclerotic plaques (Rus, Vlaicu, & Niculescu, 1996). The main source of IL-8 in these plaques is macrophages (Apostolopoulos, Davenport, & Tipping, 1996), with endothelial and smooth muscle cells also contributing (Dje N'Guessan et al., 2009). IL-8 may be upregulated by oxidized LDL in the endothelial wall (Dje N'Guessan et al., 2009) as well as upstream cytokines such as TNF-α (Yang et al., 2004). The role of IL-8 in atherosclerosis includes both recruitment and activation of neutrophils (Baggiolini et al., 1994), as well as monocyte adhesion to the vascular endothelium (Gerszten et al., 1999). IL-8 has been shown to increase in response to a high fat

meal in some (Esser et al., 2013) but not all (Esposito et al., 2003; Myhrstad et al., 2011) studies when measured. Discrepancies may be due to the higher energy and total fat content of the meal in the study reporting an increase in IL-8 postprandially.

A key aspect of the initial stages of atherosclerosis is the adhesion of inflammatory cells, mainly leukocytes, to the vascular endothelium. Two important adhesion molecules shown to have implications in the development of atherosclerosis state are VCAM-1 (De Caterina et al., 1997) and ICAM-1 (Collins et al., 2000). These molecules are measured in the blood after they have been detached from the endothelium and are circulating in their soluble form. VCAM-1 and ICAM-1 are expressed on the endothelial surface of the blood vessel wall (Carlos et al., 1990) and upregulated in response to increased concentrations of several pro-inflammatory cytokines (Gimbrone, Cybulsky, Kume, Collins, & Resnick, 1995). These adhesion molecules enable the adhesion and penetration of leukocytes across the vascular endothelium (Carlos et al., 1990). Some evidence suggests that increases in soluble adhesion molecules may only be present in an already pro-atherosclerotic environment (O'Brien et al., 1993), such as diabetic (Ceriello et al., 2004) and hypertriglyceridemic (Rubin et al., 2008) individuals. Postprandial increases in cellular adhesion molecules in healthy subjects have been shown to be small (Nappo et al., 2002) or nonexistent (Gill et al., 2003; Tsai, Li, Lin, Chao, & Chen, 2004). However, both ICAM-1 and VCAM-1 have been reported to predict future cardiovascular events in patients with coronary artery disease (Ridker et al., 1998).

Interleukin 10 (IL-10) is an anti-inflammatory cytokine produced by Th2 cells and macrophages (Wakkach et al., 2000). Its role in atherosclerosis is largely based around its anti-inflammatory effect on macrophages (Bogdan et al., 1991). IL-10 has been shown to be inversely correlated with CRP in human patients and increased levels of IL-10 are associated with

decreased risk for myocardial infarction and death (Heeschen et al., 2003). Currently, little literature exists on the postprandial response of IL-10 to a HFM.

Chronic Physical Activity and PPL

Physically active individuals have a lower postprandial lipemic response compared to less active individuals (Cohen et al., 1989; Merrill et al., 1989). Mechanisms often attributed to the triglyceride lowering effects of chronic physical activity include increased post-exercise LPL activity (Herd, Kiens, Boobis, & Hardman, 2001), increased HDL concentrations (Patsch, Karlin, Scott, Smith, & Gotto, 1983), and replenishment of intramuscular triglycerides (IMTG) (Kiens & Richter, 1998). In one experimental study, subjects who completed a jogging program 3-days/week displayed significantly higher pre-heparin plasma LPL concentrations when compared to their own control condition at baseline (Miyashita et al., 2010). It has also been demonstrated in healthy subjects given a high-fat meal that there is an inverse relationship between HDL-C and PPL (Patsch et al., 1983). Additionally, most benefits of exercise training on blood lipid values, including HDL-C, can be achieved in the absence of weight loss (Thompson et al., 1988). Therefore the mechanisms increasing HDL-C level may be independent of negative long-term energy balance.

The benefits of exercise training, even in the most active individuals, may be short-lived. Herd et al. (2000), for example, showed that after 60 hours without exercise, there was no difference in PPL between trained and untrained subjects. This study compared highly active individuals with varied exercise training to individuals who participated in no more than two, 30-minute exercise sessions per week. After being at least 60 hours removed from their last bout of exercise, there were no significant differences in postprandial triglycerides between endurance-trained, strength-trained, and untrained participants. Physiological adaptations to detraining, such

as reduced aerobic capacity, occur over a much longer time period than 60 hours (Neufer, 1989). Therefore, mechanisms independent of aerobic capacity are the likely drivers of exercise attenuated PPL.

Kiens & Richter, (1998) investigated the effects of exercise training in endurance trained males. The study focused on intramuscular triglycerides (IMTG) and their use during post-exercise recovery and discussed the possible role of lipoprotein lipase (LPL) in this process. The authors found that IMTG stores were diminished post-exercise until 42 hours. LPL activity was significantly increased the day following exercise, but returned to baseline levels at 42 hours post-exercise. These data suggest circulating TRLs could possibly be broken down by increased LPL activity and used to replenish IMTG stores and provide fuel for post-exercise recovery. When LPL activity is returned to baseline levels and IMTG stores are replenished, the attenuating effect of previous exercise on PPL appears to be diminished.

Another mechanism that may reduce the effect of a previous exercise bout is calorie replacement. An active individual is likely to replace at least some of the calories expended during their last about of exercise, and replacement of the energy expended during a bout of exercise may negate the attenuation of PPL (Burton et al., 2008). In combination, these findings may help explain why lipid-lowering effects of an exercise training program appear to be so brief. Further details into these short-term adaptations to exercise will be discussed below.

Despite the apparent brevity of several of the PPL-lowering adaptations from exercise, there does appear to be some benefit of prior training status with regard to PPL. In a study performed by Tsetsonis, Hardman, & Mastana (1997), trained and untrained (VO_2 max 50.3±5.9, 31.7±3.6 ml/kg/min respectively) middle-aged women completed a bout of walking exercise of similar duration and intensity (90 min at 60% VO_2 max), 16h prior to ingestion of a high-fat

meal. There was no significant difference in lipemia between groups after their non-exercise control sessions, but trained subjects had a 30% reduction in lipemia when compared to untrained women the morning after the exercise session (Tsetsonis et al., 1997). However, since the relative exercise intensity of each group was the same, but the aerobic capacity of the trained group was higher, the trained group achieved a greater overall energy expenditure. The role of energy balance and PPL will be discussed in more detail later.

Exercise Timing and PPL

It appears that exercise performed during the timeframe between 18 hours pre-meal, until around 90 minutes postprandially may be effective in attenuating PPL. Gill et al. (2004) showed exercise in the 12-18 hour range prior to ingestion of a high-fat meal attenuated the lipemic response to a high-fat meal. Additionally, Zhang et al. (2004) showed an attenuation of PPL in subjects that exercised 12 hours, but not 24 hours prior to a high-fat meal. Several years prior, Zhang, Thomas, & Ball (1998), showed exercise performed immediately before ingestion of a high-fat meal was also effective at attenuating PPL. Collectively, this evidence reinforces the idea that pre-meal exercise benefits on PPL are relatively acute. However, evidence also supports exercise during the postprandial period as effective for attenuation of PPL. It has been demonstrated that exercise performed as much as 90 minutes following ingestion of a meal is effective for attenuating PPL (Hardman & Aldred, 1995; Katsanos & Moffatt, 2004).

The mechanisms for exercise induced attenuation of PPL may be slightly different depending on the timing between the bout of exercise and the meal ingested. Exercise performed well in advance of the meal (12-18h) may attenuate PPL via increased LPL expression on the surface of the vascular endothelium (Kiens, Lithell, Mikines, & Richter, 1989). LPL expression in response to exercise appears to increase between 4-8 hours post-exercise (Seip &

Semenkovich, 1998), returning to baseline levels around 20 hours post-exercise (Seip, Mair, Cole, & Semenkovich, 1997), which may explain the lack of PPL attenuation by exercise performed 24h before the meal. Exercise performed immediately before the meal may attenuate PPL due to a decreased hepatic secretion of VLDLs (Sondergaard et al., 2011). Prolonged exercise is thought to reduce fatty acid synthesis, increase fatty acid oxidation and cause accumulation of triglyceride in the liver in response to prolonged exercise. It has also been shown that circulating VLDL concentrations are decreased at 4.5 hours post-exercise under post-absorptive conditions (Borsheim, Knardahl, & Hostmark, 1999). Therefore, it is possible that for exercise performed before a high-fat meal, PPL attenuation is initially due to decreased hepatic VLDL secretion and as more time passes between the exercise bout and meal ingestion, LPL activity gradually becomes a greater factor leading to greater triglyceride clearance from circulation.

PPL lowering mechanisms for post-meal exercise appear to be similar to that of pre-meal exercise. A small but significant amount of circulating triglyceride may contribute to total energy expenditure during exercise; however, the absolute rate of VLDL oxidation is not different than under resting conditions (Sondergaard et al., 2011). Additionally, greater blood flow through the vasculature during exercise leads to increased contact time between triglyceride and LPL and more opportunity for triglyceride to be hydrolyzed. Last, in a similar manner to pre-meal exercise, post-meal exercise may decrease hepatic fatty acid synthesis and reduce VLDL accumulation in the bloodstream (Sondergaard et al., 2011).

Exercise Energy Expenditure, Intensity and Energy Balance and PPL

Energy Expenditure

Exercise frequency, intensity, duration, and energy expenditure are all important considerations for an overall exercise program. When specifically targeting attenuation of PPL, overall energy expenditure may be the most influential factor to consider. In a previous review by Petitt & Cureton, (2003), authors concluded that the magnitude of prior exercise induced energy expenditure appears to directly determine the magnitude of PPL attenuation.

Individual research studies have attempted to determine a threshold for energy expenditure needed to attenuate PPL. Studies have used energy expenditures in excess of 1000kcal (Tsetsonis & Hardman, 1996b) to attenuate PPL, however, these studies may not represent an energy expenditure that is realistic for most individuals to achieve regularly. Energy expenditures of this magnitude are most likely only achieved by highly trained individuals with aerobic capacities exceeding that of the general population. However, evidence suggests that obese individuals and those with lower aerobic capacities may need less exercise energy expenditure to attenuate PPL. In support of this hypothesis, it has been shown in sedentary men that both pre-meal exercise of less than 500kcal and a postprandial walk of 30 minutes are effective for attenuating postprandial triglycerides (Murphy, Nevill, & Hardman, 2000; Klein et al., 1992). Other studies have demonstrated that moderately active individuals may need energy expenditures in the 600-900kcal range in order to attenuate PPL (Gill et al., 2004; MacEneaney et al., 2009; Brandauer et al., 2013). Therefore, it appears that individuals at lower physical activity levels may need to expend less energy during exercise to attenuate PPL. However, as individuals experience increases in physical activity and aerobic capacity, their energy expenditure threshold to attenuate PPL may also increase over time.

Intensity

Exercise intensity, duration, and overall energy expenditure are all dependent on one another. As the previous section indicated, total energy expenditure appears to have the strongest correlation with attenuation of PPL. It has been shown that low intensity exercise performed the evening before (15h prior) to a high-fat meal was effective at attenuating PPL (Aldred, 1994). However, to achieve an adequate energy expenditure to attenuate PPL at a low intensity, this bout of exercise took two hours to complete. Exercise of this duration would be unattainable for most individuals attempting to lower their non-fasting triglycerides. When low intensity exercise was performed for only 90 minutes, no attenuation of PPL was shown (Tsetsonis & Hardman, 1996a). Moderate intensity exercise has been shown to attenuate PPL with a duration more representative of typical exercise habits. Zhang et al., (1998) showed one hour of moderate intensity exercise (60% VO_2 max) was effective at attenuating PPL when performed one hour or 12 hours prior to a high-fat meal. To further support the benefits of moderate intensity exercise, studies have shown as little as 30 minutes of brisk walking at a moderate intensity can be effective at attenuating PPL (Murphy et al., 2000; Miyashita et al., 2008). Both of these studies compared continuous exercise to shorter, intermittent bouts and found both types of exercise to be equally effective. Both of these studies represent exercise sessions that may be more suitable for a typical adult who may cite time concerns as a reason for not exercising.

Although postprandial exercise has been less frequently studied compared with pre-meal exercise, similar exercise intensities appear to be beneficial for both timeframes. Moderate intensity exercise in the postprandial period has been shown to be effective for attenuating PPL (Katsanos & Moffatt, 2004). Low intensity exercise in the postprandial period has produced mixed results; some researchers have shown lower intensity exercise to be effective for attenuating PPL (Hardman & Aldred, 1995), others have not (Welle, 1984). In a similar manner

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to pre-meal exercise, 90 minutes of low intensity exercise was required to lower PPL, however, exercise of this duration may not represent a true-to-life approach for attenuating PPL. Overall, despite studies using a wide range of exercise intensities attenuating PPL, it appears that exercise of moderate intensity may be most appropriate due to the impractical time commitment required for low intensity exercise and the inability of many individuals to perform higher intensity exercises particularly in the time period around consumption of a meal.

Energy Balance

Studies over the last few decades have shown prior exercise to be an effective way to attenuate PPL (Gill, Herd, & Hardman, 2002; Herd et al., 2001). However, fewer studies have investigated how attenuation of PPL may be altered by replacing the energy deficit created by the bout of exercise. When subjects replaced 110% of the calories expended during exercise with a meal replacement drink, the triglyceride lowering effects of the bout of exercise were no longer present (Burton et al., 2008). These results were supported by another study in which subjects performed a long, exhaustive bout of exercise and either remained in energy balance or replaced oxidized carbohydrates with a high-glycemic-load drink. The authors found that postprandial triglycerides were not attenuated when subjects consumed the carbohydrate replacement beverage following exercise (Harrison et al., 2009). Collectively, data suggest that overall energy balance plays a key role in the attenuation of PPL**.**

The comparative roles of diet-induced versus exercise-induced energy deficit has also been investigated**.** Using a novel study design, Maraki et al. (2010), examined energy deficit through dietary restriction alone, exercise induced, or a combination of both. Results indicated that all three groups had an attenuated PPL response. However, the exercise induced energy deficit group had the greatest attenuation of PPL even though the diet restriction + exercise

group had a slightly more negative energy balance. These findings are in partial agreement with a study by Gill & Hardman, (2000) that found a non-significant reduction in postprandial triglycerides by energy restriction alone. The latter study found an exercise induced energy deficit to be three times as effective as energy restriction alone at attenuating PPL. Maraki & Sidossis, (2010) reviewed studies and concluded that for aerobic exercise to be effective for reducing PPL, an energy deficit of around 7kcal/kgbw is required.

Chronic Physical Activity and Systemic Inflammation

As more research has established atherosclerosis as an inflammatory disease, many studies have examined the relationships between long-term physical activity habits, aerobic fitness, and systemic inflammation. Highly active individuals typically display lower levels of circulating systemic inflammation, compared to low-active individuals. In a study by Fischer, Berntsen, Perstrup, Eskildsen, & Pedersen, (2007), eighty-four healthy adults were divided into four groups based on their presence or absence of obesity and their physical activity status. The authors found elevated levels of IL-6 and CRP in inactive individuals even when controlling for obesity, age, gender, and smoking status. These results suggest that obesity and physical activity are independent but additive risk factors for increased levels of IL-6 and CRP. In agreement with these findings, large epidemiological studies have found inverse relationships between physical activity and several pro-inflammatory biomarkers, including IL-6 and TNF-α (Panagiotakos, Pitsavos, Chrysohoou, Kavouras, & Stefanadis, 2005; Shanley et al., 2013). Exercise intervention trials, however, have been less conclusive regarding beneficial effects of physical activity on inflammation markers. A meta-analysis found a non-significant reduction of CRP of only 3% from exercise intervention trials (Kelley & Kelly, 2006). Thus it appears short-term exercise interventions may not be effective at significantly reducing inflammation, but high

levels of physical activity appear to result in lower levels of systemic inflammation long-term (Kasapis & Thompson, 2004).

Most studies examining the physical activity/inflammation relationship have focused on measuring inflammation in the fasted state. Since much of the developed world spends the majority of their day in the postprandial state, research has examined the associations between physical activity and the postprandial inflammatory response. Dixon, Hurst, Talbot, Tyrrell, & Thompson, (2009) conducted a study investigating the relationship between long term physical activity status and postprandial inflammation. Subjects were split into active and inactive groups. Active subjects were required to have participated in greater than 90 minutes of vigorous activity per week and 30 minutes of moderate activity 5 days/week. Inactive subjects engaged in no vigorous activity and 30 minutes of moderate activity less than 5 days/week. Results showed active subjects had lower glucose, insulin, and triglyceride concentrations, but no differences in postprandial inflammatory markers between groups. Based on these data, the authors suggested that there may be other contributing mechanisms to postprandial inflammation and not simply related to the increase in postprandial lipemia and glycemia.

The Anti-Inflammatory Effect of Acute Exercise

The relationship between chronic levels of physical activity and systemic inflammation has been well established. However, the precise mechanisms behind the inflammatory response to an acute bout of exercise are still being investigated. IL-6 has been extensively studied as both a pro- and anti-inflammatory cytokine. Previous research has shown IL-6 released from contracting skeletal muscle may increase nearly exponentially (up to 100 fold) throughout a bout of exercise (Steensberg et al., 2000). As exercise intensity and duration increase, so does the increase in circulating IL-6.

IL-6 released from skeletal muscle appears to be anti-inflammatory and has been shown to increase lipolysis and fat oxidation without an increase in triglycerides (Van Hall, 2003). Increased IL-6 production has an inhibitory effect on both TNF-α and IL-1, both of which are considered pro-inflammatory (Steensburg, Fischer, Keller, Moller, & Pedersen, 2003). IL-6 has also been shown to increase the production of IL-10, a cytokine well known for its anti-inflammatory effects on the body (Steensburg et al., 2003). Additionally, IL-10 has been shown to inhibit the production of many pro-inflammatory cytokines including: IL-1β, TNF-α, and IL-8 (Pretolani, 1999). Taken together these mechanisms could explain the anti-inflammatory effects of IL-6 secreted by skeletal muscle during exercise.

Acute Exercise and Postprandial Inflammation

The effects of an acute bout of exercise on postprandial inflammation is relatively unknown. Experimental studies aimed at reducing postprandial inflammation through exercise have mostly focused on moderate to high-intensity pre-meal exercise (MacEneaney et al., 2009; Brandauer et al., 2013). While these studies found prior exercise to be effective at attenuating PPL, they have no found acute exercise to be effective at decreasing postprandial inflammation. Other mechanisms, in addition to PPL may be responsible for the pro-inflammatory environment seen after a high-fat meal. Experimental studies have examined the relationship between prior exercise and markers of oxidative stress and endothelial function postprandially (Gabriel et al., 2012; Tyldum et al., 2009; Gill et al., 2004). These studies have shown that bouts of moderate and high-intensity exercise may be able to diminish or prevent any increases in oxidative stress and endothelial dysfunction caused by a high-fat meal. This may be due to an increase in anti-oxidant capacity during exercise. This hypothesized mechanism is supported by Gomez-Cabrera, Domenech, & Vina, (2008) who showed a high antioxidant status in subjects who regularly

exercised. Together, it appears that moderate to high-intensity aerobic exercise prior to a high-fat meal is effective at attenuating PPL, oxidative stress, and endothelial function. However, these bouts of prior exercise have not had beneficial effects on postprandial pro-inflammatory cytokine concentrations.

Future studies should examine postprandial exercise as a modality to reduce postprandial inflammation. Currently, there have been no studies that have measured postprandial cytokine concentrations when the bout of exercise was also performed postprandially. The anti-inflammatory effect of IL-6 released from skeletal muscle during the bout of moderate exercise may provide an effective stimulus to attenuate the rise in postprandial cytokines often seen after a high-fat meal. Postprandial exercise may also improve triglyceride clearance by increasing exposure of circulating triglyceride to LPL on the vascular endothelium through increased blood flow. Reduced hepatic secretion of VLDLs during exercise may provide an additional triglyceride lowering and anti-atherogenic mechanism behind postprandial exercise.

Conclusion

As societies around the world have developed and food has become more abundant, more time is now spent in the postprandial period than ever before. It is well known that a prolonged elevation of circulating triglycerides promotes an atherogenic environment, as demonstrated a number of times through postprandial inflammation following a single high-fat meal.

Atherosclerosis was once thought to be a disease of excess blood lipids, but is now known to be very closely linked to a number of pro-inflammatory pathways inside the vascular endothelium. A modality consistently shown to reduce circulating triglycerides, as well as inflammation, is physical activity. Highly active individuals have lower fasting and non-fasting triglycerides than low active individuals, and also exhibit lower levels of circulating

inflammatory markers. However, few studies have shown an acute bout of exercise prior to the meal consumption to be effective at attenuating both circulating triglycerides and inflammation.

Previous literature examining exercise and postprandial inflammation has focused on a bout of exercise 12-18 hours prior to ingestion of the HFM without caloric replacement. Prior exercise in this time-range has been shown to be an effective way of attenuating PPL, but there appears to be a disconnect between PPL and postprandial inflammation. Previous studies have shown postprandial pro-inflammatory cytokine concentrations to be no different between exercise and non-exercising groups when studied acutely. Therefore, future research should focus on reducing pro-inflammatory cytokines in addition to lowering PPL.

Many studies examining the relationship between a high-fat meal and postprandial inflammation have used a standard meal between 1500-2300 kcal, a meal size not representative of a normal individual's diet. In the present study, the goal was to investigate a more true-to-life approach to the interaction between diet and exercise on postprandial inflammation. The high-fat meal in the current study consisted of a commercially available breakfast bowl with portion sizes more representative of a meal an individual may consume on their own.

Postprandial exercise may lower postprandial lipemia through mechanisms not present during pre-meal exercise. Postprandial exercise increases blood flow through capillary beds increasing circulating triglyceride contact time with LPL on the endothelium. Also, similar to pre-meal exercise, postprandial exercise decreases hepatic VLDL synthesis. Postprandial exercise may use intramuscular triglycerides as a direct fuel source and use circulating triglycerides may to replenish these IMTG stores during exercise. Additionally, a unique aspect of postprandial exercise is the anti-inflammatory effect of IL-6 being released from skeletal muscle as the high-fat meal is being digested and absorbed into the bloodstream. In order to test

the effectiveness of postprandial exercise on PPL and inflammation, a moderate intensity walk was performed 60 minutes following the ingestion of the high-fat meal with an energy expenditure equal to half of the calories ingested in the high-fat meal. This represents an intensity and duration individuals of varying aerobic capacities could complete following a meal without gastrointestinal upset. Collectively, these unique aspects of the current study represent a fresh approach to attenuating PPL and inflammation caused by a high-fat meal.

Therefore, the aim of this study was to investigate the potential of postprandial exercise as a modality to reduce PPL and postprandial inflammation. We chose a meal with a more true-to-life caloric content as compared to previous PPL studies. Additionally, we focused on moderate intensity exercise for a duration that may be reasonable in the post-meal period. We hypothesized that a bout of moderate intensity postprandial exercise would increase triglyceride clearance and reduce postprandial inflammation as compared to remaining sedentary in the postprandial period.

Chapter 2 - Methods

Participants

Forty college-aged participants were recruited for this study. Thirty-nine subjects (age 25.1±5.4 yrs; 19M 20F) completed the study. One participant dropped out because of failure to complete the meal in the allotted time. All subjects were healthy, non-smokers, none of whom reported any cardiovascular or metabolic disorders as assessed by a medical history questionnaire. Participants were recruited via word of mouth and fliers around campus. To be eligible to participate, participants had to either meet or exceed physical activity guidelines ($\geq$ 150 minutes of moderate to vigorous physical activity (MVPA) per week) or participate in < 30 minutes of MVPA per week as measured by a short-form International Physical Activity Questionnaire (IPAQ). Written and verbal consent were obtained from all subjects. The study was approved by the Institutional Review Board Involving Human Subjects at Kansas State University, and conformed to the Declaration of Helsinki.

Experimental Design

Participants visited the laboratory on two separate occasions with a minimum of eight days and no more than twenty-one days between visits. During the first visit subjects completed medical history and physical activity questionnaires. Then participants underwent anthropometric measurements that included height, weight, waist circumference, and body fat percentage. Participants then completed a treadmill incremental test to exhaustion ($VO_{2\ peak}$) to determine their aerobic capacity and the duration of exercise to be performed on the second visit day if they were randomized to the exercise (EX) group. Participants were then fitted with an Actigraph GT3X accelerometer (Actigraph, Pensacola, FL, USA), worn at the wrist at all times except showering, to assess physical activity for the seven days leading up to the second

laboratory visit. All participants were asked to keep a detailed three day food log prior to their second laboratory visit. They were also asked to pick up a standardized, prepackaged frozen meal the day before their second laboratory visit and eat the meal twelve hours before their appointment and fast until their arrival. Participants were asked to document any part of the standard meal they did not consume. Participants were asked to abstain from caffeine, alcohol, or exercise for at least 24 hours prior to their second visit.

Participants usually arrived for their second laboratory session between 7:00-9:00 am to begin data collection. A catheter was inserted via antecubital vein and blood samples were drawn to be measured for triglycerides, glucose, and cholesterol. After these measurements were complete, the remaining blood sample was centrifuged and plasma samples were pipetted into cryovials and stored at -60 degrees C. After baseline blood sampling procedures subjects then had 20 minutes to consume the HFM (described below). Immediately afterward, the HFM subjects provided a resting metabolic rate measurement, which was then repeated 200 min post-HFM. Additional blood draws were performed at 2 and 4 hours post-HFM. Randomization by a random number generator occurred after participants signed up for the study, but was not revealed to them until after the exercise test. Participants were randomized to either the control (CON) condition, in which the subjects were asked to remain sedentary throughout the postprandial period, or the exercise (EX) condition in which the subjects performed a moderate intensity walk at 60% of their VO_{2peak} for a duration that would require them to expend half of the calories consumed from the high-fat meal (HFM). Subjects in the exercise condition began walking 60 minutes after the last bite of their meal. The timing of exercise, blood draws, and resting metabolic rate measurements was designed so that there would be no time overlap between data collection procedures.

Tests and Measurements

Anthropometric Measures

All anthropometric measurements were completed by a trained research assistant. Before any measurements were taken participants were asked to remove shoes and any outer clothing and jewelry that could be easily removed. Height was measured with a SECA 214 portable stadiometer (Invictus Plastics, Leicester, England) to the nearest 0.1cm, and weight was measured with a digital scale (Pelstar LLC, Alsip, IL, USA) to the nearest 0.1kg. Waist circumference was measured with Gulick spring loaded measuring tape (Accufitness, Greenwood Village, CO, USA) at the horizontal plane of the iliac crest. All measurements were taken twice, and a third measurement was taken if height differed by more than 0.5cm or weight by 0.5kg. The two values closest to each other were averaged and used for analysis. Body fat percentage was measured via dual energy X-ray absorptiometry (DEXA) scan (GE Lunar Prodigy, Madison, WI, USA).

Questionnaires

All participants completed a previously validated IPAQ form (Dinger, Behrens, & Han, 2006). This questionnaire asks participants to recall their physical activity behavior for the last seven days. Physical activity is categorized into vigorous, moderate, walking, and sitting time. All participants noted how many of the prior seven days they had participated in each one of those behaviors and how much time on average did they spend in each behavior per day.

3-Day Food Log

A 3-day food log was used to determine total dietary calories and macronutrient distribution. Subjects were trained on how to fill out the diet record properly and were asked to complete entries for the three full days (2 weekdays and 1 weekend day) before their second visit

to the laboratory. Upon arrival to the laboratory for their second visit, subjects reviewed their

diet records with a trained research assistant who would subsequently enter the dietary

information into computer software to eliminate any confusion or possible mistakes on the

entries. The 3-day food record was then entered by the research assistant into Nutritionist Pro

nutrient analysis software version 5.2.0 (Axxya Systems-Nutritionist Pro, Stafford, TX). Data

generated from the food logs included total energy intake, as well as macronutrient distribution

and totals.

Peak Aerobic Capacity

An incremental exercise test to exhaustion on a treadmill (Precor 932i, Woodinville,

WA,USA) was performed to asses peak aerobic capacity. Heart rate was measured using a (Polar

Wear Link Coded) chest strap heart rate monitor. Substrate oxidation was assessed via breath

analysis of O_2 consumption and CO_2 production (Parvomedics TrueOne 2400 Metabolic Cart,

Sandy Utah). The Borg scale rating of perceived exertion (RPE) from 0-20 was used to assess

perceived effort at the end of each stage. Participants warmed up for four minutes at their own

pace and the incremental protocol began at a subjects' fastest self-perceived 5 kilometer pace at a

2% incline. Speed was increased by 0.5 mph every two minutes, and beginning at the fourth

stage (6 minutes into the test), speed was increased by 0.5 mph and incline was increased by 1%

at the beginning of each stage. Heart rate and VO_2 were continuously reported and RPE was

recorded 30 seconds prior to the end of each stage. It was determined that participants had

achieved VO_{2peak} when their heart rate was within $\pm$ 1SD of age predicted maximal heart rate

(200-age), respiratory exchange ratio > 1.10, or if the participant was unable to continue. VO_{2peak}

was recorded was the highest 15-second average measurement over the duration of the test.

High-Fat Meal

The HFM consisted of 10kcal/kg of body weight (Jimmy Dean's Meat Lovers Breakfast Bowl); 63% fat calories. Subjects were instructed to ingest the entire meal within 20 minutes of their first bite. The nutritional composition of the meal was 460 calories per bowl, 33 grams of fat, 265mg of cholesterol, 17g of carbohydrate, and 24g of protein. Total kilocalories consumed ranged from 450 to 1113, with fat content ranging from 32.2 to 79.8g. All but one subject was able to complete the meal within the allotted time; one dropout cited intense dislike for the taste and texture of the provided meal.

Blood Samples

Blood samples were taken at baseline prior to consumption of the HFM, and 2 and 4 hours after the HFM. Blood draws were completed by flushing the catheter with a 3ml syringe and drawing the whole blood sample through a 5 ml syringe (BD, Franklin Lakes, NJ, USA). The whole blood samples were deposited into a 6ml K2 EDTA BD Vacutainer (BD, Franklin Lakes, NJ, USA). Alere Cholestech LDX Lithium Heparin Capillary Tubes capillary tubes were used to draw blood from the vacuum tubes for lipid analysis (Cholestech LDX Analyzer, Alere San Diego Inc., San Diego, CA). The remaining blood in the vacuum tube was centrifuged by a CxR Centrifuge (LW Scientific, Lawrenceville, GA, USA) and plasma samples were immediately pipetted into cryovials (Fisher, Hanover Park, IL, USA) and stored at -60 degrees C. After all subjects had completed the experimental protocol, plasma samples were shipped to Eve Technologies (Calgary, Alberta, Canada) to be analyzed. In this study we quantified 7 biomarkers using three different custom-plex assays. A Human High Sensitivity Cytokine 5-Plex, a Human Neurodegenerative Panel 2 Single Plex and a Neurodegenerative Panel 3 Single Plex. The multiplex assays were performed according to their protocol at Eve Technologies by

using the Bio-Plex™ 200 system (Bio-Rad Laboratories, Inc., Hercules, CA, USA). The

cytokine 5-plex consisted of IL- 1β, IL-6, IL-8, IL-10, and TNFα with assay sensitivities ranging

from 0.11 – 0.48 pg/mL. The Neurodegenerative Panel 2 single plex consisted of CRP with assay

sensitivity of 0.0022ng/mL. The Neurodegenerative Panel 3 single plex consisted of sICAM-1

and sVCAM-1 with assay sensitivity being 6.44pg/mL.

Resting Metabolic Rate (RMR)

RMR was measured by indirect calorimetry using a ventilated metabolic hood

(Parvomedics TrueOne 2400 Metabolic Cart, Sandy, Utah). Subjects were instructed to lie down

on a bed with their head resting on a pillow as metabolic hood was placed over their head.

Subjects were instructed to remain as still and relaxed as possible over the duration of the 30

minute measurement. The first five minutes of the RMR measurement was discarded for each

participant to allow the CO_2 concentration under the hood to be adjusted to ≈1% where it was

maintained through the duration of the measurement by a trained research assistant. Data were

collected from the most consistent 20 minutes of the RMR session. Data collected from the RMR

session included macronutrient utilization, resting energy expenditure, and estimated energy

expenditure during the duration of the RMR session.

Post-HFM Exercise

Subjects randomized to the EX group were instructed to begin walking on the treadmill

exactly 60 minutes after completion of their meal. Subjects were pre-fitted with a heart rate

monitor strap. Exercise was performed within + or – 5 bpm of their heart rate at 60% VO_{2peak}

under close supervision of a research assistant. The duration of the exercise was based on the

amount of time it took subjects to burn half of the calories consumed in their high-fat meal. This

was calculated using the following equation:

$$\frac{bwkg \times 10\ calories \times 50\%\ of\ calories\ consumed}{\left(\left(\left((VO2peak \div 1000) \times bwkg\right) \times \frac{4.825kcal}{liters\ oxygen}\right) \times 60\%VO2peak\right)}$$

Statistical Analysis

Data analyses were conducted using IBM SPSS Statistics v22.0 (IBM Corporation, Armonk,NY). Pearson's r and Spearman's rho 2-tailed correlations were performed to assess associations between independent and dependent variables, as well as between PPL and inflammatory markers for parametric and non-parametric data respectively. Comparisons between EX and CON groups were performed using a two-way analysis of variance where condition was the between-subjects factor and time (baseline, 2 hours, and 4 hours) was the within-subjects factor. If parametric assumptions were not met, data were transformed (Lg10) and subsequent tests were performed. For data that could not be appropriately transformed, appropriate non-parametric tests were used to compare EX and CON groups Friedman's tests with Mann-Whitney U for between subject's tests for each time point were performed. Independent samples t-tests were used to determine differences between individual times. For all analyses, significance was set at $p{<}0.05$.

Chapter 3 - Results

Participant Characteristics

Participant characteristics are shown in Table 3.1. Thirty-nine participants (19M, 20F) completed the duration of the study. Thirty-six participants completed all blood draw procedures; we were unsuccessful inserting catheters in the three remaining participants. Participants were aged (25.1±5.4yrs), BMI (25.5±5.1), body fat % (27.10±12.56) with no differences between the walking (EX) and the no-walking group (CON).

Table 3.1 Participant Characteristics

		Postprandial Condition	
	All Subjects	**EX**	**CON**
Sex	19M; 20F	9M; 10 F	10M; 10F
Age (years)	25.10±5.43	25.79±5.91	24.45±4.99
Height (cm)	171.12±10.36	171.29±10.36	170.96±10.64
Weight (kg)	75.12±16.72	74.36±15.91	75.84±17.83
BMI (kg/m^2)	25.5±5.1	25.4±5.5	25.7±4.8
Body Fat (%)	27.10±12.56	28.34±12.15	25.93±13.15
VO$_{2peak}$ (ml/kg/min)	47.14±11.60	47.57±12.67	46.72±10.76

*Data are presented as mean±SD. There were no differences between groups.

Energy Balance

Energy balance data are shown in Table 3.2. The average amount of energy consumed was 751±167.4 kcals, with no significant difference between groups. The average exercise energy expended on the treadmill in the EX group was approximately half of the energy consumed in the meal (377.8±79.6 kcals). Estimated energy balance at 4hr included resting

energy expenditure at baseline extrapolated out to 4hr postprandially. The time the EX group

spent exercising was not included in the equation and exercise energy expenditure was added to

the calculation separately.

Table 3.2 Energy Balance Characteristics

		Postprandial Condition	
	All Subjects	**EX**	**CON**
Energy consumed	751.0±167.4	743.6±159.1	758.4±178.3
Energy expended on treadmill (EX only)	181.1±196.1	377.8±79.6	N/A
Energy balance at 4hr (Baseline REE included)	293.2±194	123.7±61.6	462.7±114.4

*All data presented as kcals; mean±SD.

Metabolic Data

Mean values for blood lipids and glucose are presented in Table 3. There were no

differences between the EX and CON groups at baseline for glucose, TRG, HDL, LDL, or TC.

TRG significantly increased over time ($F=56.952$, $p<0.001$) with no differences between groups

($F=0.027$, $p=0.871$), however HDL decreased across time ($F=17.279$, $p<0.001$) in both groups.

An independent samples t-test showed HDL to be different at 2hr ($p=0.049$), but not at any other

time points. LDL significantly decreased across time ($F=30.539$, $p<0.001$) and there were no

differences between EX and CON groups ($F=0.537$, $p=0.471$). For total cholesterol (TC) there

was a condition-by-time interaction as a quadratic function ($F=10.350$, $p=0.003$). The EX group

increased TC at 2hr before returning to baseline at 4hr, the CON group decreased TC at 2hr

before returning to baseline at 4hr.There were no between group differences for EX and CON

over time ($F=0.466$, $p=0.499$), nor any differences between groups for any individual time

points. For glucose, there was a condition-by-time interaction that was a quadratic function (F=39.484, p<0.001). The EX group increased glucose at 2hr before returning to baseline at 4hr, the CON group decreased glucose at 2hr before returning to baseline at 4hr. There were no across-time differences between EX and CON groups (F=3.457, p=0.071). However, there was a group difference for glucose at 2hr (p<0.001).

Table 3.3 Metabolic Data at Baseline, 2hr, and 4hr

	Baseline		2 Hours		4 Hours	
	EX	**CON**	**EX**	**CON**	**EX**	**CON**
TRG (mg/dL)	70.9±29.2	69.1±28.3	112.4±42.5*	115.1±62.1*	140.0±59.4*	152.0±89.8*
HDL (mg/dL)	51.2±13.2	47.7±11.1	50.9±12.9^	43.6±8.5*	47.8±12.4*	42.7±8.3*
LDL (mg/dL)	81.3±17.8	96.4±33.3	74.9±16.8	81.4±27.2	66.89±17.2	76.2±27.0
TC (mg/dL)	143.4±23.9	153.1±30.6	148.5±24.1*#	147.1±26.6	142.9±21.1	154.85±34.8
Glucose (mg/dL)	86.1±10.4	86.9±6.5	93.6±7.9*^#	80.8±9.3*	85.6±7.6	85.1±6.5

*Indicates a change from baseline. ^Indicates a difference between groups; # indicates a condition-by-time quadratic change. All significance set at (p<0.05). All data are presented as mean±SD. All data were normally distributed except LDL and glucose at baseline.

Table 3.4 Lg10 Transformed Metabolic Data at Baseline, 2hr, and 4hr

	Baseline		2 Hours		4 Hours	
	EX	**CON**	**EX**	**CON**	**EX**	**CON**
TRG	1.82±0.17	1.81±0.16	2.02±0.17	2.00±0.23	2.11±0.19	2.12±0.24
HDL	1.70±0.12	1.67±0.10	1.70±0.12	1.63±0.09	1.67±0.12	1.62±0.09
LDL	1.90±0.09	1.96±0.14	1.86±0.10	1.89±0.15*	1.81±0.12*	1.86±0.16*
TC	2.15±0.08	2.18±0.08	2.17±0.07	2.16±0.07	2.15±0.06	2.18±0.09
Glucose	1.93±0.06	1.94±0.03	1.97±0.04	1.90±0.05	1.93±0.04	1.93±0.03

*Indicates a change from baseline; ^Indicates a difference between groups; # indicates a condition by time quadratic change. All significance set at (p<0.05). All data are presented as mean±SD. All data are normalized except glucose at baseline.

Figure 3.1 Metabolic Responses to a HFM

a.

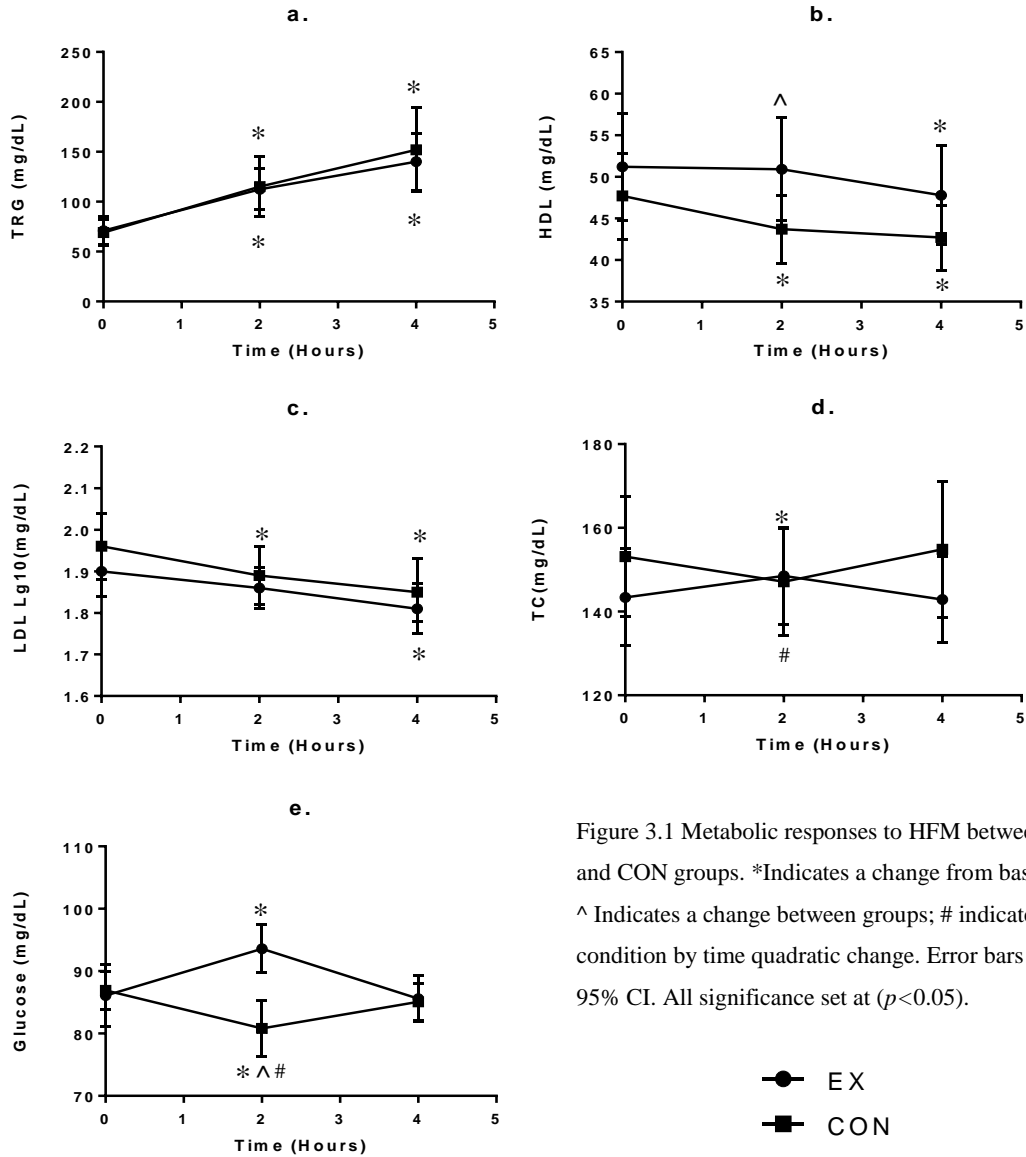
b.

c.

d.

e.

Figure 3.1 Metabolic responses to HFM between EX and CON groups. *Indicates a change from baseline; ^ Indicates a change between groups; # indicates a condition by time quadratic change. Error bars indicate 95% CI. All significance set at ($p<0.05$).

● EX
■ CON

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Inflammatory Data

Plasma cytokine data are presented in Table 4. There were no differences between EX and CON for any cytokines at baseline ($p>0.05$). IL-1β decreased across time ($F=10.774$, $p=0.003$) with no differences between EX and CON groups ($F=0.165$, $p=0.687$). IL-6 was significant as a quadratic function ($F=9.206$, $p=0.005$), decreasing from baseline to 2hr and returning to baseline at 4hr with no difference between conditions ($F=1.231$, $p=0.276$) across time. There was a significant condition by time interaction as a quadratic function for IL-6 ($F=4.239$, $p=0.048$). An independent samples t-test revealed a difference between groups for IL-6 at 2hr ($p=0.039$) but not any other timepoint. IL-8 decreased across time ($p=0.006$) with no differences between groups (all time points $p>0.05$).There were no changes for IL-10 across time ($F=2.762$, $p=0.107$) with no differences between groups ($F=1.122$, $p=0.298$). TNF-α decreased across time ($F=9.035$, $p=0.006$) with no differences between EX and CON groups ($F=1.077$, $p=0.310$). Cellular adhesion molecules were only measured at baseline and 4hr. There were no differences between groups for sICAM-1 across time ($F=0.818$, $p=0.372$). There was a significant increase in sVCAM-1from baseline to 4hr ($p=0.035$) with no differences between groups (all time points $p>0.05$). However, a related samples t-test analysis showed sVCAM-1 increasing in the EX group from baseline to 4hr ($p=0.003$), the CON group did not ($p=0.831$).

Table 3.5 Inflammatory Markers

	Baseline		2 Hours		4 Hours	
	EX	CON	EX	CON	EX	Con
hs-CRP (mg/L)	13.1±27.1	22.7±36.69				
IL-1β (pg/ml)	3.26±1.91	3.29±2.09	2.82±1.3*	2.71±1.74	2.49±1.02	2.74±1.88
IL-6 (pg/ml)	0.76±0.51	0.75±0.53	0.52±0.37	0.84±0.64	1.0±0.71	1.25±1.15
IL-8 (pg/ml)	5.57±1.22	4.90±1.44	4.27±1.88	4.52±1.58	4.29±1.98	4.40±1.86
IL-10 (pg/ml)	4.67±2.79	4.70±3.10	3.74±3.18	4.52±3.51	3.52±2.27	5.35±4.75
TNF-α (pg/ml)	5.22±2.24	4.99±2.35	3.85±2.58	4.42±2.35	4.78±2.40	4.07±2.55
sICAM-1 (ng/ml)	79.72±22.52	72.83±15.13			78.76±27.65	70.11±13.52
sVCAM-1 (ng/ml)	585.42±125.58	599.30±150.11			632.76±134.96	598.14±141.08

*Indicates a change from baseline. ^Indicates a difference between groups. All significance set at ($p<0.05$). TNF-α was the only marker that was normally distributed. hs-CRP was only measured at baseline, sICAM-1 and sVCAM-1 were only measured at baseline and 4hr. All data are presented as mean±SD.

Table 3.6 Lg10 Transformed Inflammatory Markers

	Baseline		2 Hours		4 Hours	
	EX	CON	EX	CON	EX	Con
hs-CRP	0.61±0.69	0.69±0.83				
IL-1β	0.47±0.19	0.44±0.28	0.39±0.25*	0.35±0.29*	0.35±0.22	0.32±0.378
IL-6	-0.18±0.23	-0.23±0.31	-0.39±0.33*^	-0.16±0.27	-0.11±0.33	-0.06±0.40
IL-8	0.74±0.08	0.66±0.20	0.54±0.37	0.62±0.21	0.55±0.33	0.58±0.29
IL-10	0.62±0.21	0.58±0.29	0.45±0.35	0.56±0.28	0.47±0.27	0.58±0.38
TNF-α	0.67±0.23	0.62±0.33	0.39±0.56	0.57±0.28	0.59±0.33	0.50±0.35
sICAM-1	4.89±0.11	4.85±0.10			4.87±0.15	4.84±0.09
sVCAM-1	5.76±0.11	5.77±0.10			5.79±0.11	5.77±0.09

*Indicates a change from baseline ($p<0.05$). ^Indicates a difference between groups. All significance set at ($p<0.05$). hs-CRP, IL-1β, IL-6, IL-10, and sICAM-1 become normally distributed; TNF-α, IL-8, and sVCAM-1 are not normally distributed. hs-CRP was only measured at baseline, sICAM-1 and sVCAM-1 were only measured at baseline and 4hr. All data are presented as mean±SD.

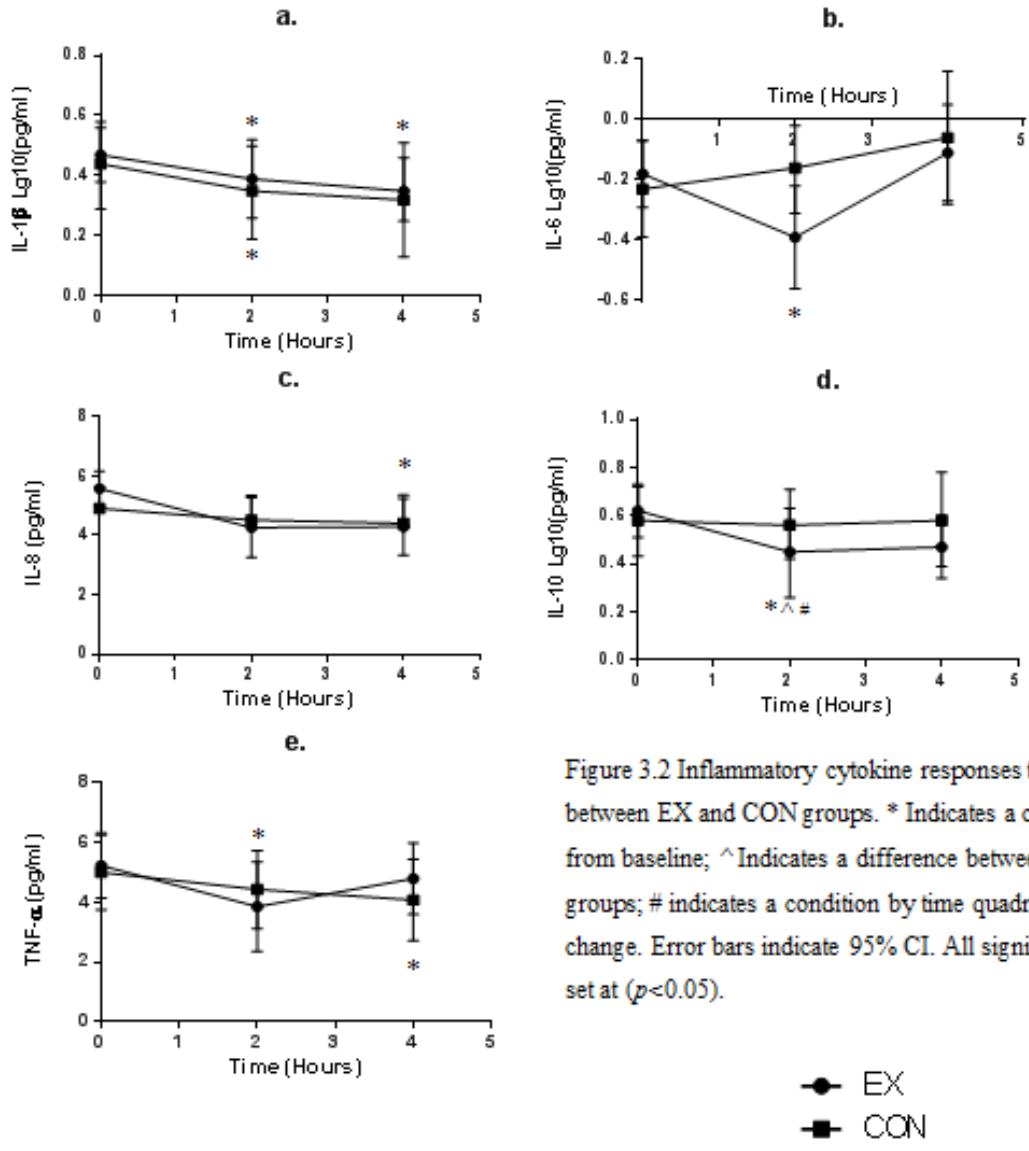**Figure 3.2 Inflammatory Cytokine Responses to a HFM**

Figure 3.2 Inflammatory cytokine responses to HFM between EX and CON groups. * Indicates a change from baseline; ^ Indicates a difference between groups; # indicates a condition by time quadratic change. Error bars indicate 95% CI. All significance set at ($p<0.05$).

Figure 3.3 Cellular Adhesion Molecules after a HFM
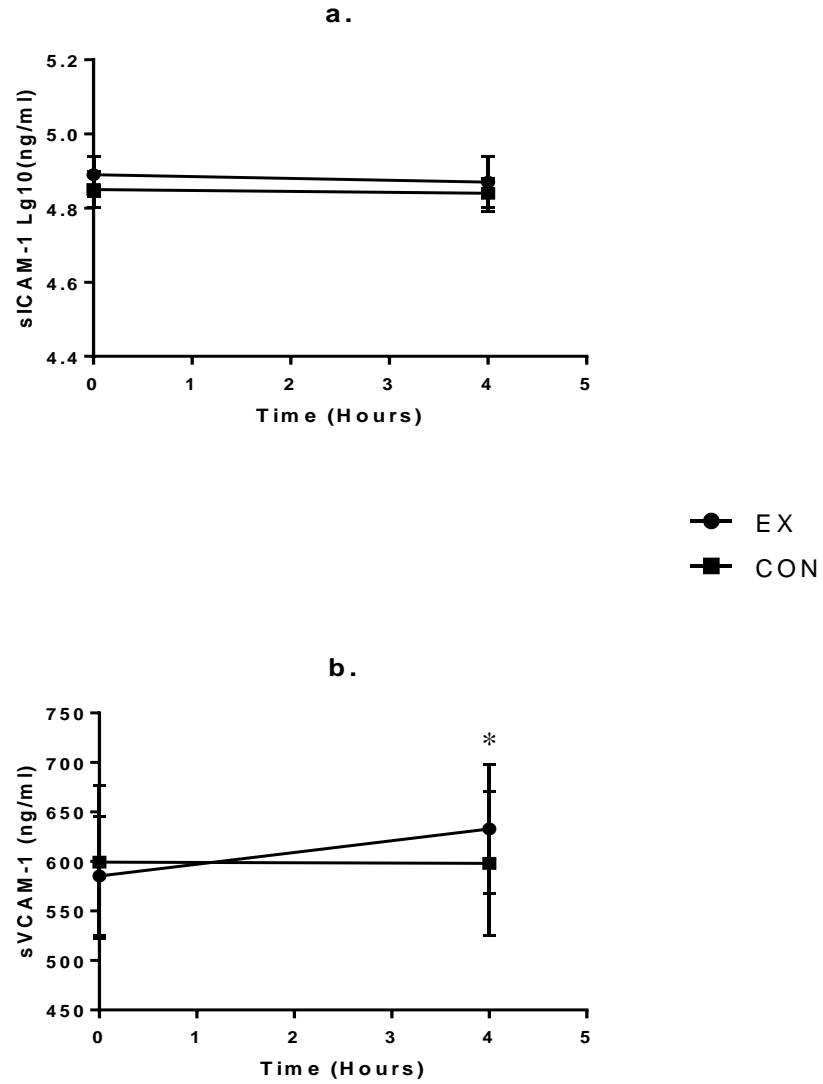

a.

b.

Figure 3.3 Cellular adhesion molecule responses to HFM between EX and CON groups. * Indicates a change from baseline. Error bars indicate 95% CI. Significance set at ($p<0.05$).

Associations Between Factors Previously Shown to Affect inflammation

A Pearson correlation showed body fat percentage was associated with CRP at baseline ($r=0.694$, $p<0.001$) and with IL-6 at baseline, 2hr, and 4hr ($r=0.447$, $r=0.458$, $r=0.439$ respectively, $p<0.01$). VO$_{2peak}$ was inversely correlated with CRP at baseline ($r=-0.560$, $p<0.001$) and inversely correlated with IL-6 at baseline and 2hr ($r=-0.516$, -0.491 respectively, $p<0.01$). VO$_{2peak}$ was associated with sVCAM-1 ($r=0.518$, $p=0.001$) at 4hr. There were no other associations between independent and dependent variables ($p>0.05$).

Associations Between TRG and Inflammatory Markers

Pearson correlation analysis revealed an association between changes in TRG and IL-10 from 0-2hrs ($r=0.467$, $p=0.007$). No other associations were found between change in TRG and change in any inflammatory markers. However, when controlling for VO$_{2peak}$ through a partial correlation, change in TRG was associated with change in TNF-α ($r=0.508$, $p=0.016$), IL-6 ($r=0.469$, $p=0.028$), IL-8 ($r=0.590$, $p=0.004$), and IL-10 ($r=0.538$, $p=0.010$) from baseline-2hr. There were no other change scores that were significantly associated when examining the relationship between PPL and inflammation for changes from baseline to 2 and 4hrs.

When body fat was added as another controlled variable in the partial correlation analysis, change in TRG was once again associated with change in TNF-α ($r=0.527$, $p=0.014$), IL-6 ($r=0.465$, $p=0.034$), IL-8 ($r=0.575$, $p=0.006$), and IL-10 ($r=0.479$, $p=0.028$) from baseline to 2hr. When controlling for body fat percentage and VO$_{2peak}$, there were no other change scores that were significantly associated between PPL and inflammation for changes between baseline and 2 and 4hrs.

Chapter 4 - Discussion

Major Findings

The purpose of this study was to investigate a more true-to-life approach to lowering the postprandial rise in circulating triglycerides and inflammation following a HFM. This was investigated with a study design that had young, healthy, participants walk at a moderate intensity for the duration of time needed to expend half of the calories they consumed in a HFM. This combination of meal and exercise was intended to represent a real-to-life scenario that individuals may regularly engage in. Our first hypothesis predicting an attenuation of PPL in the EX group was not supported. Our results show, in disagreement with previous literature, moderate intensity exercise in the postprandial period did not attenuate the postprandial rise in triglycerides. Our second hypothesis anticipated a reduction in postprandial inflammation in the EX group due to the expected attenuation of PPL. The lack of inflammation in either condition supports the results of previous studies that have shown a disconnect between PPL and postprandial inflammation. Additionally, participants who performed a moderate intensity bout of exercise one hour after the HFM did not reduce postprandial inflammation as compared to participants who remained sedentary in the postprandial period.

Metabolic Findings

As expected, postprandial triglycerides increased significantly ($\approx$100%) from baseline at both 2 and 4hrs postprandially. However, there were no differences between the EX and CON groups at any time point. This is in disagreement with previous literature that has demonstrated moderate intensity exercise in the postprandial period to be effective at attenuating PPL (Hardman & Aldred, 1995; Katsanos & Moffatt, 2004). A key difference between the current study and previous studies that have investigated postprandial exercise is the exercise energy

expenditure. Both of the aforementioned studies used exercise protocols that required participants to exercise at a light to moderate intensity for 90 minutes. One of the main goals of the current study was to implement a more real-to-life exercise protocol that a typical individual may be able perform on a regular basis. The EX group had an energy expenditure of approximately 5kcal/kgbw. One previous review concluded an exercise induced energy deficit of around 7kcal/kgbw is required for aerobic exercise to effectively attenuate PPL (Maraki & Sidossis, 2010). Our study used a postprandial bout of exercise while the previously mentioned review examined energy deficits via diet and exercise the day prior to a HFM. A postprandial bout of exercise to reach this energy deficit would not meet the "true-to-life" goal of the current study. These data suggest that a true-to-life bout of exercise in the postprandial period may not produce a large enough energy expenditure or negative energy imbalance to attenuate PPL.

Additionally, the wide variance of aerobic capacities of the participants for the current study may have been the cause for such a highly varied lipemic response. The EX and CON groups both had participants of varying aerobic capacities and initial statistical analyses did not control for the possible effect of aerobic capacity on PPL. However, secondary data analyses revealed that when VO_{2peak} was dichotomized into high and low groups, there were no between group differences over time for PPL (data not shown). In sedentary populations, individuals with lower aerobic capacities may require lower energy expenditures and shorter walking bouts to lower PPL as compared to more active individuals (Murphy et al., 2000; Klein et al., 1992). In our study, the wide range of endurance capacities may have affected the relationship between the bout of exercise and PPL at 2 and 4hrs. This hypothesis was supported by our data that showed lower mean triglycerides at four hours in the EX group, but a high variability among both groups for all triglyceride time points made statistical significance difficult to achieve. An effect size

was calculated using means and SD (d=0.1568), representing a small to no effect on TRG by the EX condition.

While we did not see differences between the EX and CON groups from postprandial TRGs, we did see significantly higher HDL concentrations in the EX group when compared with the CON group. Higher HDL concentrations are in agreement with previous studies that have shown exercise training was associated with higher HDL concentrations (Thompson et al., 1988). Patsch et al. (1983) demonstrated an inverse relationship between HDL and PPL. This relationship is supported by the current study that showed an inverse correlation between the change in HDL and TRG concentrations from 2hr to 4hr, the time period where there was the greatest decrease in HDL concentration occurred. Increased PPL and decreased HDL across time supports previous work that explains a prolonged elevation of TRLs after a HFM may increase the lipid exchange between TRLs and HDL (Lamarche et al.,1999). This lipid exchange allows HDL particles to be easily cleared from circulation by the liver.

Similarly to HDL, LDL concentrations were decreased across time in both the EX and CON groups. However, LDL was not directly measured; the Cholestech LDX Analyzer uses the Friedewald formula (LDL=TC-HDL-(TRG/5) to calculate LDL concentrations. Therefore the sharp rise in TRG among both the EX and CON groups may have been the primary cause of decreased LDL seen in both groups.

Changes in TC concentrations are likely due to changes seen in individual lipoprotein subfractions. The condition by time quadratic function seen between groups may have been due to the group difference in HDL at the 2hr time point. There were no differences between TRG or LDL between groups at any time point, so it would appear that higher HDL in the EX group is the primary cause of the condition-by-time interaction for TC. Previous literature has shown

reductions in TC, HDL, and LDL after a HFM (Tsai et al., 2004) and therefore, changes in blood lipids seen in the current study are in agreement with those previous findings.

Glucose was significantly higher in the EX group at the 2hr time point. Increases in glucose appearance in the blood stream during exercise relative to a sedentary condition may have been the primary reason behind this difference between groups. However, measuring blood glucose at 2 and 4hrs postprandially may not have fully allowed us to explain what group interactions were occurring because glucose concentrations can change so quickly in the blood.

Inflammatory Findings

Inflammatory measures in the postprandial period are mixed throughout the literature. The main findings from our study were no differences in inflammatory markers between EX and CON groups over time. Traditional pro-inflammatory cytokines did not increase (IL-6), or decrease (TNF-α, IL-8, IL-1β) across time with no difference between groups. IL-10, an anti-inflammatory cytokine, also decreased across time without group differences. Most previous literature shows inflammatory cellular adhesion molecules sICAM-1 and sVCAM-1 to respond similarly in the postprandial period. However, this study only found an increase in sVCAM-1 that was largely driven by the EX group. There was no change in sICAM-1 across time in either group.

IL-6 showed a significant change as a quadratic function as a time by condition interaction. The quadratic change was the result of the EX group decreasing in IL-6 concentration from baseline to 2hr while the CON group showed a small non-significant increase. Neither group was different from baseline at the 4hr time point. The decrease in IL-6 from baseline to 2hr before returning to baseline at 4hr is a pattern that has been seen in previous literature. Lundman et al. (2009) found IL-6 concentrations to be decreased at the 2hr time point

before increasing above baseline values at 4 and 6hr postprandially. IL-6 may have been elevated at 4 and 6hrs postprandially because the standard meal used was 1000kcal, much larger than the average energy intake of participants in our current study. The larger energy consumption in the Lundman study may explain the difference in IL-6 at 4hr. Miglio et al. (2013) also found an increase in IL-6 across all time points from 2hr to 8hr, but also provided a meal with a much higher energy intake (1416kcal) than the meal in the current study. The time course of IL-6 may indicate our HFM did not provide enough of an inflammatory stimulus to increase IL-6 at any time point, or it could be argued that only measuring IL-6 at 2 and 4hr postprandially missed a potential rise in IL-6 after our final blood draw took place. The latter circumstance was demonstrated by Poppitt et al. (2008) when IL-6 was not increased at 1 or 3hrs postprandially, but was increased at 6hr. Our study did found a significant time by condition interaction for IL-6 as a quadratic function. Lower IL-6 in the EX group at 2hr may support an acute anti-inflammatory effect of exercise as discussed by Petersen & Pedersen, (2005).

The decrease in TNF-α in the current study is fairly consistent with most literature that has found no change (Poppitt et al., 2008) or a slight decrease (Payette et al., 2009) in TNF-α across several time points. There were no differences between groups for TNF-α and it does not appear as though it was influenced by exercise, but does appear to be related to IL-6.

 IL-1β was decreased across time with no differences between groups. In healthy subjects, such as in the present study, IL-1β has not changed in response to a HFM (Cheng et al., 2011). Decreased IL-1β would again suggest the HFM given to our participants was not enough to elicit a pro-inflammatory response.

IL-8 was also found to decrease over time with no difference between groups. IL-8 concentrations in the current study were similar to previous studies that provided meals of

similar energy intake. Esser et al. (2013) used a meal of ≈ 950kcals and found IL-8 to increase postprandially, but the same study found a meal of more moderate energy intake (400kcal) had no effect on IL-8. Myhrstad et al. (2011) gave participants a meal of ≈ 700kcal and also found no change in IL-8 concentrations. Therefore, it appears that changes in IL-8 postprandially may only be induced by meals with much higher energy loads than the meal provided in the current study.

Little previous literature exists on IL-10 responses to a high-fat meal, but decreased IL-10 postprandially as seen in our study would suggest a pro-inflammatory state. However, this finding contradicts the rest of the inflammatory data in the current study that does not demonstrate an inflammatory environment. IL-10 would be expected to increase after myokine secreted IL-6 during exercise (Petersen & Pedersen, 2005), however, no increase in IL-6 at any time point may partially explain no changes in IL-10 across time between EX and CON groups.

Postprandial cellular adhesion molecule data was mixed; sICAM-1 did not change across time in either group, but sVCAM-1 was increased at 4hr with no differences between groups at either time point. However, the EX group appears to have driven the increase in sVCAM-1 by increasing from baseline to 4hr while the CON group did not. Increased sVCAM-1 in the EX group is in agreement with previous literature that has shown small increases in cellular adhesion molecules immediately following moderate exercise (Jilma et al., 1997). On the other hand, previous HFM literature shows no increases in postprandial adhesion molecules in healthy subjects in most (Gill et al., 2003; Tsai et al., 2004), but not all (Ceriello et al., 2004) studies. Thus it appears that sVCAM-1 may be increased due to the bout of exercise and not the HFM. This is supported by our data that show increases in sVCAM-1 across time in the EX group only, even though no time by condition interactions were found.

Associations between PPL and Inflammation

Previous research has linked increased postprandial TRG and inflammation. Our study has shown a possible disconnect between the increase in postprandial TRG and increased inflammation. TRG were associated with TNF-α at baseline, but not any other marker of inflammation at any time point. When controlling for body fat percentage and VO_{2peak}, associations between change scores showed changes in TRG from baseline to 2hr were associated with changes in several inflammatory markers over the same time period, but these relationships were no longer present between any other time points. Despite the substantial rise in TRG at both 2 and 4hr postprandially, our participants showed little sign of a pro-inflammatory state at either time point. In agreement with Brandauer et al. (2013) and previous work in our lab group (Kurti et al., 2015; Ade, Rosenkranz, & Harms, 2014) our study demonstrates that the postprandial inflammatory process is very complex and may be initiated by several factors other than increases in postprandial TRG alone. Previous studies that have shown increases in postprandial inflammation may have done so by inducing metabolic and oxidative stress through a large overall energy intake. It is possible that increases in postprandial TRG and inflammatory markers may be dependent on the meal itself and yet independent of one another.

Experimental Considerations

A major strength of this study was the "true-to-life" approach to the HFM and postprandial exercise bout. Most previous studies have either used meals that exceeded the energy intake typically consumed in one sitting and/or used a standardized meal given to participants regardless of body weight. The meal in the current study consisted of 10kcal/kgbw (751.0±167.4kcal). This meal size would be more typical of an amount that an individual may eat for breakfast on a typical day. The food provided was also breakfast food containing a

mixture of eggs, potatoes, sausage, bacon, and cheese rather than foods used in previous studies that would not typically be consumed at breakfast. This meal allowed us to measure postprandial inflammation under similar metabolic conditions as would be seen on a day to day basis. In accordance with the "true-to-life" approach to the test meal, participants were allowed one hour to digest their meal before the EX group performed a moderate intensity walk that lasted (39.18 ± 11.75 min) and expended (371.82 ± 79.58kcal) of energy. This bout of exercise was represented an intensity, duration, and energy expenditure that many individuals would be able to regularly complete, particularly in the postprandial period. Designing the study with less extreme metabolic conditions did not allow us to answer a mechanistic question related to a HFM more or diet-exercise interactions, but it did allow us to apply prior mechanistic research to circumstances that may be more relevant to diet and physical activity guidelines used by health professionals.

Limitations

The postprandial response to blood lipids and inflammatory markers is very complex and highly variable among participants. Our study only collected blood and plasma samples at two time points in the postprandial period. Many previous studies in this area of the literature have measured blood lipid and inflammatory markers at a greater number of time points over a longer period of time. The design of our study may have resulted in missed potential changes in blood and plasma data that could have been seen at the one hour or three hour postprandial time points. Additional changes could have also occurred at time points beyond four hours and these would have not been measured in our study.

Additionally, there was a large variation of aerobic capacities of the participants in this study. This approach to recruitment allowed statistical analyses to examine the effect of aerobic

capacity on PPL and postprandial inflammation. However, the wide range of aerobic capacities made it more difficult to detect an effect from the bout of exercise on PPL and inflammation. Most of the data collected in the study had a large variance which made it more difficult to detect statistical significance between EX and CON groups. More homogenous participant groups may be able to better isolate the effect of postprandial exercise on blood lipids and inflammatory markers.

The "true-to-life" approach to the HFM and exercise bout may make the results of our study more applicable to the general population, but the smaller meal size in comparison to other HFM studies may not have been a large enough inflammatory stimulus to truly examine the effect of postprandial exercise on the inflammatory markers measured. With consumption of 10kcal/kgbw there were virtually no signs of a pro-inflammatory state among the participants who remained sedentary in the post-prandial period. This may not have allowed the bout of exercise to exert any anti-inflammatory effects because the body was not in a pro-inflammatory state to begin with. The participants in the current study were young adults with no known metabolic diseases, many of whom were highly active and had much higher aerobic capacities than a typical individual. The generally low metabolic risk participants in our study most likely resulted in a lower rise in postprandial triglycerides and a lesser inflammatory response to the HFM, as compared to a higher-risk group of participants. Although the development of atherosclerosis has been shown to occur early on in life, evidence of this slowly developing inflammatory disease may not be shown by the postprandial response to a single meal in young healthy subjects, particularly with caloric and fat intakes which are more typical for a breakfast that would be consumed by an adult. Even though the meal given to our participants was high in

fat (63% fat) and resulted in a large increase in postprandial triglycerides, the moderate overall caloric content of the meal may explain the lack of postprandial inflammation.

Future Directions

The findings of the current study suggest that a single HFM, when portioned to the size of a typical breakfast, does not induce an inflammatory response. The lack of inflammatory response from the meal may not have allowed the moderate intensity bout of exercise to exert any anti-inflammatory effects on a system that had not been metabolically challenged to begin with. The evidence to support HFM induced inflammation has been well established, but our study suggested that among individuals with low metabolic risk, an unusually large energy and fat containing meal may be required to create this inflammatory state. Future studies should focus on populations with higher metabolic risk (advanced age, obese, abnormal blood lipids, sedentary, etc.) and determine if a true-to-life HFM is enough of a stimulus to induce postprandial inflammation.

Conclusion

This study demonstrates that following a true-to-life breakfast, participants who engaged in a moderate bout of postprandial exercise did not have attenuated PPL or altered markers of postprandial inflammation when compared to participants who remained sedentary in the postprandial period. Additionally, in healthy individuals with low metabolic risk, a HFM adjusted for body weight does not induce postprandial inflammation despite a substantial increase in postprandial triglycerides. These data suggest that previous studies that have shown increases in postprandial inflammation after a HFM have used meals that contain much more energy than a typical individual would consume in one setting. Studies that have shown reduced lipemia through postprandial exercise have used exercise bouts of long duration and energy

expenditure that a typical individual is not likely to engage in on a regular basis, particularly on workdays and immediately following a meal. Pro-inflammatory, pro-atherogenic phenotypes are more likely to develop due to long term positive energy balance (weight gain) and chronic sedentary behavior than from a single HFM followed by several hours of sedentary behavior.

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