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Exercise Intensity and Postprandial Lipemia

La intensidad del ejercicio y la lipemia postprandial

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Abstract. Exaggerated postprandial lipemia has been observed in metabolic and cardiovascular diseases and is associated with increased risk for cardiovascular disease (CVD). Prior aerobic exercise reduces the triglyceride response to a high-fat meal. The purpose of this review is to examine the factors contributing to metabolic dyslipidemia and to review available evidence supporting the role of aerobic exercise in reducing postprandial lipemia. The contribution of exercise intensity and excess-post exercise oxygen consumption (EPOC) to changes in postprandial lipemia is examined.
Key words. lipemia, Metabolic Syndrome, exercise, EPOC

Resumen. La exagerada lipemia postprandial exagerada ha sido observada en enfermedades metabólicas y cardiovasculares, y está asociada a un mayor riesgo de enfermedad cardiovascular (ECV). Se ha encontrado que el ejercicio aeróbico previo reduce la respuesta de los triglicéridos a una comida rica en grasas. El propósito de esta revisión es examinar los factores que contribuyen a la dislipidemia metabólica y revisar la evidencia disponible que respalda el papel del ejercicio aeróbico en la reducción de la lipemia postprandial. Se examina la contribución de la intensidad del ejercicio y el exceso de consumo de oxígeno post-ejercicio (EPOC) en los cambios en la lipemia postprandial.
Palabras claves. lipemia, Síndrome Metabólico, ejercicio, EPOC

Introduction

The combination of increased dietary intake, sub-optimal physical activity, and increased overweight and obesity has placed Americans at an elevated risk for the development of metabolic diseases. In 2008, CVD accounted for 33% of deaths in America, and remained the leading cause of mortality among men and women (Roger et al., 2011). Approximately 27% of the population met the criteria for Metabolic Syndrome (MetS) in 2000, this percentage significantly increased from 23% in 1994 (Ford, Giles, & Mokdad, 2004). Those with MetS possess elevated risk for the development of CVD, Type 2 Diabetes and Stroke (Kolovou et al., 2005; Wannamethee, Shaper, Lennon, & Morris, 2005). Despite multiple available definitions, abdominal obesity and insulin resistance are key features thought to underlie MetS, and subsequently CVD risk (Kassi, Pervanidou, Kaltsas, & Chrousos, 2011; Reaven, 1995).

In middle-aged overweight adults, following adjustment for traditional risk factors, non-fasting triglycerides remain a significant predictor of CVD, while fasting triglycerides do not (Bansal et al., 2007; Patsch et al., 1992). Exposure of the vascular endothelium to triglyceride-rich lipoprotein (TRL) particles and their remnants promotes atherosclerosis and is fundamental in the etiology of CVD (Hodis & Mack, 1998; Zilversmit, 1979, 1995). For certain individuals, including those with MetS, hypertension, CVD and type 2 diabetes, non-fasting triglycerides remain elevated above healthy control values for 6 to 8 hours following a meal, increasing exposure of the vasculature to atherogenic particles (Kolovou et al., 2005; Kolovou et al., 2003; Kumar, Madhu, Singh, & Gambhir, 2010). While multiple factors contribute to the development of postprandial lipemia, insulin resistance, associated with metabolic conditions such as MetS and CVD, has been shown to contribute to hypertriglyceridemia (Ginsberg, Zhang, & Hernandez-Ono, 2005).

A recent expert panel statement indicated that a desirable postprandial triglyceride response to a high-fat meal is no higher than 220 mg/dl (Kolovou et al., 2011). Based on these guidelines, even otherwise-healthy overweight control subjects may display elevated postprandial lipemia in response to a high-fat meal (Patsch et al., 1992). Because non-fasting triglycerides are not typically measured in the general population, CVD risk for many individuals who are exposed to postprandial lipemia may be underestimated. Additionally, Salazar et al. (Salazar et al., 2011) have shown that 60% of men not meeting the criteria for MetS were insulin resistant, defined as those in the top 25% of fasting plasma insulin concentration. In the same group of subjects, insulin resistant participants who did not have diagnosable MetS had a significantly higher BMI, e.g. 27 vs. 24.9 kg/m^2 than non-insulin resistant subjects (Salazar et al., 2011). Other reports have shown that even normal weight individuals may be insulin resistant (McLaughlin, Allison, Abbasi, Lamendola, & Reaven, 2004). Thus overweight and normal weight subjects without diagnosable metabolic disease may be insulin resistant and, as a result, be prone to secondary dyslipidemia. Aerobic exercise serves as a non-pharmacologic therapeutic intervention that lessens postprandial lipemia, and may substantially reduce cardiovascular disease risk.

Dyslipidemia

Dyslipidemia is a common feature of atherosclerotic diseases including MetS and can be characterized by elevated triglycerides, an increased number of small, dense LDLC particles, and low HDLC (Kathiresan et al., 2006; Park, Kim, Lee, & Park, 2011). Elevations in triglyceride observed with insulin resistance and MetS are associated with increases in VLDL particle size and number (Adiels, Olofsson, Taskinen, & Boren, 2008; Kissebah, Alfarsi, Adams, & Wynn, 1976; Lucero et al., 2012; Tan et al., 1995). The large, triglyceride-rich VLDL produced under conditions of insulin resistance serve as precursors to atherogenic small, dense LDLC particles that are slowly degraded (Demant & Packard, 1998). The combined effects of elevated plasma triglycerides in conjunction with increased activities of hepatic triglyceride lipase (HTGL) and cholesterol ester transfer protein (CETP) result in small, dense HDLC particles that are rapidly cleared from the circulation, and atherogenic small, dense LDLC (Demant & Packard, 1998; Morton, 1999; Sandhofer et al., 2006; Xiao et al., 2008).

A large body of evidence confirms that elevated triglycerides and reduced HDLC are significantly associated with CVD risk (Austin, Hokanson, & Edwards, 1998; Gordon et al., 1989; National Cholesterol Education Program Expert Panel on Detection & Treatment of High Blood Cholesterol in, 2002). Meta-analysis has shown that, in men, the relative risk (RR) for CVD associated with a 1 mmol/l increase in triglycerides is significant at 32% (Austin et al., 1998). Upon accounting for HDLC and other CVD risk factors, the RR was reduced to 14%, yet remained statistically significant (Austin et al., 1998). The anti-atherogenic properties of HDLC have primarily been associated with reverse cholesterol transport, and antioxidant and anti-inflammatory functions (Kontush & Chapman, 2006). In men, the CHD risk reduction associated with a 1 mg/dl increase in HDLC is approximately 2% (Gordon et al., 1989).

It has been proposed that the independent effect of elevated triglycerides in promoting CVD may be attributable to the presence of triglyceride-rich lipoprotein remnants (TRL) (Zilversmit, 1979, 1995). Lipoprotein remnants of VLDL and chylomicrons are formed as a

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result of the activity of LPL and increased triglyceride levels (Morton, 1999; Zilversmit, 1979). These remnants are rich in cholesterol ester and can be deposited in the arterial wall. Triglyceride level and remnant lipoproteins are strongly and significantly associated, and are predictive of future CVD development (Imke et al., 2005). Remnant-like cholesterol is strongly and significantly associated with carotid intima-media thickness in healthy middle-aged men, this independent of triglyceride level (Karpe et al., 2001).

Postprandial Lipemia

A recent panel statement clarified the usefulness of non-fasting triglycerides in the prediction of CVD by reviewing large-scale trials that included postprandial measurements (Kolovou et al., 2011). The results from this review indicate that the peak triglyceride response can be observed 4 hours postprandially and that this response should be less than 220 mg/dl (Kolovou et al., 2011). TRL, including chylomicrons and VLDL, are increased acutely following a meal (Cohn, McNamara, Cohn, Ordovas, & Schaefer, 1988). Chylomicrons contain predominantly apo B 48, and are secreted from the intestine postprandially, while apo B 100 containing VLDL particles are hepatically derived (Kindel, Lee, & Tso, 2010).

In those with normotriglyceridemia and hypertriglyceridemia (e.g. mean triglyceride values of 93 and 244 mg/dl, respectively) the postprandial increase in both chylomicrons and large VLDL is statistically significant (Wojczynski et al., 2011). In the same groups, chylomicrons were increased significantly following a high-fat meal, and to a significantly greater extent in those with elevated fasting triglycerides (Wojczynski et al., 2011). In healthy controls and in CAD patients with normal and elevated fasting triglycerides, there is a statistically significant increase in large chylomicrons and VLDL 3 hours following a high-fat meal (Karpe, Steiner, Olivecrona, Carlson, & Hamsten, 1993). When compared to a control group, CAD patients with hypertriglyceridemia have significantly increased large chylomicrons and VLDL at 3 and 6 hours postprandially (Karpe et al., 1993). Sedentary middle-aged men with a mean BMI of 25.7 kg/m^{-2}, and with fasting triglycerides below 221 mg/dl, display a significantly higher triglyceride AUC_I when compared to younger sedentary men with a mean BMI of 23 kg/m^{-2} (Jackson et al., 2003). In apparently healthy control subjects with a BMI above 25.0, postprandial lipid excursions have been shown to exceed the recommended cut-point of 220 mg/dl (Patsch et al., 1992). Patsch et al., (Patsch et al., 1992) have shown that healthy control participants with normal fasting triglycerides have elevated postprandial triglyceride responses of 263 and 225 mg/dl, respectively, at 4 and 6 hours. Although these values were significantly lower than a group with CVD, they are above the recommended cut-point suggested in the latest panel statement. It can be concluded that significant postprandial increases in lipoproteins are observed even in healthy weight subjects with normal triglycerides, and these increases are more pronounced in the middle aged, and in those with hypertriglyceridemia and heart disease.

Factors Influencing Metabolic Dyslipidemia

Altered activities cholesterol ester transfer protein (CETP), hepatic triglyceride lipase (HTGL), and LPL may contribute to secondary dyslipidemia by altering the composition of lipoproteins and/or affecting their clearance rate (Morton, 1999; Xiao et al., 2008). In obese subjects and in men with Met S, the mass of CETP is increased above healthy controls, and CETP activity has been shown to be increased following a meal (Arai et al., 1994; Sandhofer et al., 2006; Tall, Sammett, & Granot, 1986). In men, BMI is strongly and significantly associated with increased HTGL activity, and LPL activity is significantly reduced in obese subjects (Nie et al., 1998).

Cholesterol Ester Transfer Protein

CETP is responsible for the transfer of cholesterol ester and triglyceride between HDLC and lipids containing apoprotein B (apoB) particles including VLDL, LDLC, chylomicrons, and intermediate density lipoprotein (IDL) (Morton, 1999; Sandhofer et al., 2006). The results of increased CETP activity and hypertriglyceridemia are HDLC enriched with triglyceride and apo B particles that are enriched with cholesterol ester (Lassel, Guerin, Auboiron, Chapman, & Guy-Grand, 1998). Among Apo B containing particles, LDLC is responsible for accepting the preponderance of cholesterol ester (Lassel et al., 1998). Due, in part, to the action of CETP, the resulting triglyceride rich HDLC are cleared more rapidly from the circulation, resulting in low HDLC levels (Gazi et al., 2006; Rashid et al., 2002; Sandhofer et al., 2006; Xiao et al., 2008). Among remnant lipoproteins, VLDL particles appear to accept a greater amount of cholesterol ester than do chylomicron remnants, which may lead to an abundance of VLDL saturated with cholesterol ester (Kissebah et al., 1976; Lassel et al., 1998).

Small, Dense LDLC

HTGL plays a role in the conversion of VLDL to small, dense LDLC particles and its activity is significantly and negatively correlated with LDLC size and buoyancy (Zambon, Austin, Brown, Hokanson, & Brunzell, 1993). Small, dense LDLC has been shown to have a lower affinity for the LDLC receptor due to conformational changes in apo B 100, and therefore may be present in circulation for an extended period of time (Galeano et al., 1994). The atherogenicity of small, dense LDLC particles arises from their increased susceptibility to oxidation when compared to larger LDLC particles (Liu et al., 2002).

Oxidized LDLC particles contribute to atherosclerosis and inflammation in multiple ways, being recognized most commonly for their ability to be taken up by macrophages through scavenger receptors, leading to the development of foam cells (M. S. Brown, Basu, Falck, Ho, & Goldstein, 1980; Itabe, Obama, & Kato, 2011). In patients with CVD, the number of small, dense LDLC particles is significantly increased when compared to healthy controls, despite similar LDLC levels (Koba et al., 2006). Gazi et al, have shown that small, dense LDLC particles are increased in MetS when compared to healthy controls, and that triglyceride concentration is a significant predictor of particle number (Gazi et al., 2006). Additionally, these authors showed that, in a small sub-set of patients with MetS who had triglyceride values below 150 mg/dl, no difference was evident in mean LDLC particle size compared to healthy controls (Gazi et al., 2006). These results confirm the close association between serum triglyceride concentration and increased small, dense LDLC (Gazi et al., 2006; Kathiresan et al., 2006).

Lipoprotein Lipase

LPL is responsible for the hydrolysis of triglyceride contained in LDLC, VLDL, and chylomicrons and its activity is partially modulated by insulin (Maheux, Azhar, Kern, Chen, & Reuven, 1997; Nilsson-Ehle, Garfinkel, & Schotz, 1980). In adipose tissue, LPL activity is greater with increased insulin concentration, while in skeletal muscle, the activity of LPL is reduced under similar conditions (Kiens, Lithell, Mikines, & Richter, 1989; Kobayashi, Tashiro, Murano, Morisaki, & Saito, 1998; Sadur & Eckel, 1982). In subjects with MetS, the pre-heparin mass of LPL is significantly and positively correlated with HDLC, and significantly and negatively correlated with triglyceride, blood glucose, and body weight (Nilsson-Ehle et al., 1980; Saiki et al., 2007). Post-heparin LPL activity is significantly reduced in obese compared to lean subjects, and insulin resistant subjects have lower LPL mRNA and protein content in skeletal muscle than do non-insulin resistant controls (Arai et al., 1994; Morino et al., 2012). Sedentary, overweight, middle-aged men have significantly lower post-heparin LPL activity in both the fasted state and 9 hours following a mixed meal when compared to younger normal weight men (Jackson et al., 2003). Thus, reductions in LPL activity have been observed in obese, insulin

resistant, and overweight sedentary individuals, and likely contribute to reduced TRL clearance.

TRL are cleared in a manner that is dependent on LPL mediated hydrolysis of chylomicrons and VLDL (Nilsson-Ehle et al., 1980). The ability of LPL to hydrolyze TRL may become overwhelmed in the presence of elevated lipids (Bjorkegren et al., 1996; Brunzell, Hazzard, Porte, & Bierman, 1973). In healthy men, the administration of a chylomicron-like lipid emulsion results in substantial increases in plasma triglycerides, and linear increases in large VLDL particles (Bjorkegren et al., 1996). Following the lipid emulsion, Bjorkegren et al. (Bjorkegren et al., 1996), observed that the catabolic rate of large VLDL particles was reduced substantially when compared to a saline infusion control condition, and that the rate of conversion of large VLDL to small VLDL was decreased (Bjorkegren et al., 1996). Thus, it appears that increased chylomicrons in the plasma impede clearance of VLDL particles, and reduce the conversion of large VLDL to small VLDL. Postprandial increases in chylomicrons would lead to increases in circulating TRL and large VLDL particles.

Insulin Resistance

Insulin resistance and consequent hyperinsulinemia exacerbate hypertriglyceridemia (Ginsberg et al., 2005). In conditions of metabolic dysfunction, skeletal muscle, with adipose and hepatic tissues, may become resistant to the effects of insulin (Saltiel & Kahn, 2001). As a result, glucose uptake into skeletal muscle is decreased and insulin's ability to suppress hepatic glucose secretion may be compromised (Consoli, 1992). Plasma NEFA concentrations may be elevated due to insulin resistant adipose tissue (Kissebah et al., 1976). The elevations in plasma NEFA, in conjunction with increased glucose flux resulting from hyperglycemia, provide ample substrate for hepatic VLDL overproduction (Kissebah et al., 1976; Wu, Cappel, Martinez, & Stafford, 2010). In middle-aged men and women, the estimation of insulin resistance using the homeostatic model assessment (HOMA) score has been shown to be significantly correlated with $VLDL_1$ rate of production (Gill et al., 2004). Furthermore, when compared to lean counterparts, obese subjects have a higher VLDL secretion rate of apoB (Riches et al., 1998). It can be concluded that obesity and, specifically, insulin resistance, are associated with increased hepatic output of triglyceride-rich VLDL.

Lifestyle

Overweight and obesity, along with dietary composition and physical inactivity are associated with blood lipid abnormalities (Berg, Frey, Baumstark, Halle, & Keul, 1994; C. D. Brown et al., 2000; Lippi et al., 2006; McLaughlin et al., 2004). While insulin resistance is observed in normal weight subjects, a significant increase in BMI has been observed with increasing measures of insulin resistance, as defined as the top 25% of plasma insulin concentration (McLaughlin et al., 2004; Salazar et al., 2011). In obesity, the effect of insulin to suppress hepatic lipid assembly is compromised (McLaughlin et al., 2004). In addition, the activities of CETP and HL have been shown to be increased in obesity, while LPL activity is negatively correlated with bodyweight (Arai et al., 1994; Sandhofer et al., 2006; Xiao et al., 2008). A prospective 6.5 follow up study has shown that, with weight gain of 5% of initial body weight and final BMI of less than 30 kg/m^2, the number of large VLDL particles increases significantly, by approximately a third (Mantyselka et al., 2012). Thus even those who experience modest gains in body weight may develop secondary dyslipidemia. Elevations in postprandial lipemia are known to occur as a result of a high-fat meal, and individuals consuming a high-fat diets are exposed to postprandial lipemia as a result (Hardman, Lawrence, & Herd, 1998; Wojczynski et al., 2011). The chronic effects of overweight and obesity on dyslipidemia are coupled with the acute detrimental blood lipid alterations that occur as a result of a high fat meal.

It can be concluded that postprandial increases in triglyceride-rich VLDL and chylomicrons promote atherogenic dyslipidemia. Increases in TRL promote low HDLC and increased small, dense LDLC. Increased activity of CETP and HL contribute to this effect by creating apo B particles laden with cholesterol ester and triglyceride-rich HDLC, meanwhile facilitating the conversion of VLDL to dense LDLC (Arai et al., 1994; Sandhofer et al., 2006; Zambon et al., 1993). Reductions in LPL activity lead to compromised ability to clear TRL (Jackson et al., 2003; Zambon et al., 1993). Additionally, the effects of insulin resistance exacerbate postprandial lipemia and processes that contribute to atherogenic dyslipidemia. These alterations in enzyme activity and metabolic function that favor dyslipidemia have been described in MetS and obesity (Arai et al., 1994; Jackson et al., 2003; Sandhofer et al., 2006).

Exercise and Postprandial Lipemia

Aerobic exercise, performed 1 to 16 hours before a high-fat meal, significantly reduces postprandial triglyceride levels between 18 and 51% below non-exercise control values (Altena, Michaelson, Ball, & Thomas, 2004; Gill et al., 2006; Petitt & Cureton, 2003; Zhang, Thomas, & Ball, 1998). Studies that support these effects have used treadmill or cycling exercise of low-, moderate- , and maximal-intensity ranging from 25 to 100% of VO_2max (Freese, Levine, Chapman, Hausman, & Cureton, 2011; Gill et al., 2006; Gill, Murphy, & Hardman, 1998; Katsanos, Grandjean, & Moffatt, 2004; Mestek et al., 2008). Gill et al. (Gill et al., 2006), have shown that 90 minutes of exercise at 50% of VO_2peak performed on the day before a high-fat meal significantly reduces postprandial chylomicrons, VLDL, and remnant lipoproteins by 29, 34, and 35% when compared to non-exercise control in middle-aged overweight men. Thus, aerobic exercise is capable of reducing the postprandial increase in TRL, and substantially reducing CVD risk.

The reduction in postprandial lipemia has been shown to be related to the energy that was expended during exercise (Burton, Malkova, Caslake, & Gill, 2008; Gill, Herd, & Hardman, 2002; Tsetsonis & Hardman, 1996a, 1996b). When low- and moderate-intensity exercise is compared, regardless of intensity or duration, a threshold energy expenditure appears to exist below which alterations in postprandial lipemia are not statistically significant (Gill et al., 1998). Zhang et al. (Zhang, Ji, Fogt, & Fretwell, 2007), have shown that the postprandial reduction in triglycerides is significant following exercise at 60% of maximal capacity only after sessions where 450 calories or greater were expended, and not following a session with a 300-calorie energy expenditure. At similar exercise intensity, the postprandial triglyceride reduction is significant following caloric expenditure exceeding 800 calories, but not 400 calories (Tsetsonis & Hardman, 1996a). Mestek et al. (Mestek et al., 2008), has shown that a 500-calorie energy expenditure at 35-45 or 60-70% of maximal capacity lowers postprandial triglycerides similarly and significantly below non-exercise control. Likewise, exercise intensities of 32 and 63% of maximal capacity and equal caloric expenditure of approximately 1,000 calories lower postprandial triglycerides, with no differences between the two conditions (Tsetsonis & Hardman, 1996b). Thus, following low- and moderate- intensity exercise a caloric expenditure of 450-500 calories is sufficient to favorably alter postprandial triglycerides. It is clear that following low- and moderate- exercise, energy expenditure, instead of intensity or duration, appears to determine reductions in postprandial lipemia.

While intensity, per se, does not seem to be the primary determinant of changes in postprandial lipemia, the only studies that have directly compared exercise of differing intensities have used a narrow range of 31 to 60-70% of maximal capacity (Mestek et al., 2008; Tsetsonis & Hardman, 1996a). Furthermore, no studies have directly compared low- and high-intensity exercise. In contrast to the previously mentioned investigations, the postprandial responses to isocaloric exercise sessions at 25 and 65% of maximal capacity performed 1 hour before a high-fat meal suggest that the alterations in postprandial triglycerides following low- and moderate- intensity exercise may indeed differ (Katsanos et al., 2004). Despite similar energy expenditures of the exercise sessions,

postprandial triglycerides following exercise at 65% of VO_2peak were significantly attenuated when compared to non-exercise control, while the postprandial response following exercise at 25% of VO_2peak was similar to non-exercise control. One investigation, reporting the effects of maximal-intensity exercise on postprandial lipemia, has shown that 4 30-second all-out sprints separated by 4 minutes of active recovery significantly lower postprandial triglycerides below non- exercise control (Freese et al., 2011). The approximate caloric expenditure of this session was 287 calories, substantially below the apparent threshold of 450-500 mentioned for low- and moderate- intensity exercise. This finding may indicate that the threshold energy expenditure required for favorable alterations in postprandial lipemia is lower following maximal- when compared to moderate- or low-intensity exercise. Comparisons between low- and high- intensity exercise should be made to examine whether isocaloric exercise sessions affect postprandial lipemia differently.

Support for the hypothesis that exercise energy expenditure determines reductions in postprandial lipemia comes from studies where the energy that was expended during exercise is replaced. Three studies have reported the effects of exercise with and without energy replacement on postprandial lipemia (Burton et al., 2008; Freese et al., 2011; Harrison et al., 2009). The caloric expenditures for these studies are approximately 287, 670, and 1500 calories. The corresponding significant postprandial triglyceride reductions were 21, 14, and 40% following exercise without energy replacement when compared to non-exercise control (Burton et al., 2008; Freese et al., 2011; Harrison et al., 2009).

Burton et al. (Burton et al., 2008), has shown that exercise at 50% of maximal capacity with a caloric expenditure of 670 calories without energy replacement significantly lowers postprandial triglycerides 14% below non-exercise control, and 10% below exercise with energy replacement in obese and overweight men (mean BMI 31.1 kg/m^{-2}). The energy expended during exercise was re-fed in the form of a mixed meal. No difference in postprandial triglycerides was observed between the exercise with energy replacement trial and non-exercise control (Burton et al., 2008). When compared to non-exercise control, the postprandial insulin concentration was significantly reduced by 18 and 10% following exercise with energy deficit and exercise with energy replacement (Burton et al., 2008). There was also a 10% statistically significantly lower postprandial insulin response following exercise with energy deficit when compared to exercise with energy replacement. Of the 3 studies examining the effects of energy replacement on postprandial lipemia, this is the only experiment where investigators report a significantly different insulin response following exercise trials with and without energy replacement. This is also the only investigation to examine exercise energy replacement and postprandial lipemia in obese and overweight subjects, a population is known to be prone to insulin resistance and glucose intolerance (McLaughlin et al., 2004).

Harrison et al. (Harrison et al., 2009), provided similar results using recreationally active men with a mean BMI of 26 kg/m^2. In the energy-replacement trial, the participants were fed glucose in an amount equal to the carbohydrate utilized during exercise. Higher-intensity exercise combining continuous exercise at 70% of maximal capacity and maximal-effort bouts, and producing a 1500 calorie energy expenditure, yielded a statistically significant 40% difference in postprandial triglycerides between exercise with energy deficit and non-exercise control. A smaller, but still significant (e.g. approximately 20%) difference between exercise with energy deficit and exercise with energy replacement was also found (Harrison et al., 2009). In agreement with Burton et al. (Burton et al., 2008), no differences in postprandial triglycerides were observed between the exercise with energy replacement and non-exercise control condition. In contrast to the findings of Burton et al, (Burton et al., 2008), insulin levels did not differ across conditions. When compared to the work of Burton (Burton et al., 2008) the caloric expenditure achieved in this study is substantially greater, and the relative reduction in postprandial triglycerides much higher (e.g. 40% compared to 14%), supporting the role of energy expenditure in reducing postprandial triglycerides.

Freese et al. (Freese et al., 2011), completed a similar study using maximal intensity exercise of short duration. The caloric expenditure of the exercise session was approximately 287 calories, and was re-fed in the form of a mixed meal. Participants completed 4 maximal 30 second cycling sprints interspersed with 4 minutes of active recovery (Freese et al., 2011). The significant differences between trials for postprandial triglycerides were equal to 21% between exercise with energy deficit and non-exercise control, 12% between exercise with energy deficit and exercise with energy replacement, and 10% between exercise with energy replacement and control (Freese et al., 2011). Of the 3 studies where the energy expended during exercise has been replaced, this is the only work documenting a significantly lower postprandial triglyceride response following exercise with energy replacement when compared to non-exercise control. This may indicate a specific benefit of higher-intensity exercise on lowering postprandial triglycerides, even when the energy expended during exercise is replaced. This is one of the few studies reporting the effects of only maximal intensity exercise, and it is possible that a lower caloric expenditure is required following this type of exercise to produce significant reductions in postprandial triglycerides.

Excess Post-Exercise Oxygen Consumption

There is evidence for the effect of exercise intensity in increasing post-exercise energy expenditure (Borsheim & Bahr, 2003; LaForgia, Withers, & Gore, 2006). Following isocaloric cycling exercise of 500 calorie energy expenditure, EPOC is significantly greater after a session at 75% of VO_2max when compared to one at 50% of VO_2max (e.g. 4.8 L vs. 9 L) (Phelain, Reinke, Harris, & Melby, 1997). Even high intensity exercise of low caloric expenditure and short duration produce greater EPOC than lower-intensity exercise of longer duration (Sedlock, Fissinger, & Melby, 1989). When measured for 14 hours post-exercise, 80 minutes of cycling at 75% of maximal capacity results in a 30.1 L EPOC, compared to only 5.7 and 1.3 L following exercise for 80 minutes at 50 and 29% (Bahr & Sejersted, 1991). Gore and Withers (Gore & Withers, 1990), examined the differences in EPOC following treadmill exercise at a variety of intensities and durations. Subjects performed exercise bouts at 30, 50, and 70% of VO_2max for 20, 50 and 80 minutes (Gore & Withers, 1990). These authors found no statistically significant difference across time for the bouts at 30% of maximal capacity. Fifty minutes of exercise at 50% and 70% of VO_2max produced EPOC values of 5.19 and 10.04 L, and 80 minutes at the corresponding intensities yielded 6.10 and 14.59L (Gore & Withers, 1990). It was concluded that intensity is the primary factor determining increases in EPOC (Gore & Withers, 1990). It is evident that exercise at or above 70% of maximal capacity produces greater EPOC than exercise at or below 50% of maximal capacity. No studies have measured EPOC in order to determine its contribution to changes in postprandial lipemia. Because most studies examining postprandial lipemia have not explored higher-intensity exercise, favorable effects attributable to EPOC energy expenditure have likely been overlooked.

Potential Mechanisms

While energy expenditure has been indicated as a primary explanation for the decrements in postprandial lipemia following exercise, the precise physiological mechanisms are elusive. Increased clearance of VLDL and chylomicrons due to greater LPL activity offers one explanation for the consistent reduction in postprandial triglycerides following aerobic exercise (Greiwe, Holloszy, & Semenkovich, 2000; Kiens et al., 1989). Increases in skeletal muscle LPL activity have been observed 24 hours following running exercise at 75% VO_2max, and at as little as 4 hours after 60 minutes of knee extensor exercise at 75% of maximum capacity (Kiens et al., 1989). LPL protein content in the vastus lateralis is increased significantly 22 hours post exercise following 60 minutes of cycling exercise at 65% VO_2max (Greiwe et al., 2000).

A recent study by Al-Shayji, Caslake, and Gill (Al-Shayji, Caslake, & Gill, 2012) supports the hypothesis that in middle-aged overweight

men, the clearance of VLDL, particularly in the larger fraction, is increased on the day following exercise at 50% VO_2max. Men with a mean BMI of 31.1 kg/m^2 underwent Intralipid infusion designed to block catabolism of large VLDL particles. Following exercise, VLDL triglyceride was significantly lower, and the catabolic rates of VLDL triglyceride and apo B were significantly greater when compared to non-exercise control (Al-Shayji et al., 2012). VLDL production was not changed following the exercise or non-exercise control conditions. The composition of the VLDL particle was changed following exercise when compared to non-exercise control, with each VLDL particle containing a greater amount of triglyceride (Al-Shayji et al., 2012). The authors conclude that alterations in the composition of the VLDL particle itself may in fact lend the particle to being cleared more rapidly (Al-Shayji et al., 2012). This work strongly suggests that increased clearance of triglyceride-rich particles following exercise may explain improvements in postprandial lipemia.

Hepatic production of VLDL may decrease following a bout of exercise. A recent study using healthy normal weight women showed that, on the morning following exercise at 60% of VO_2peak where 500 calories are expended, fasting VLDL is significantly reduced when compared to non-exercise control (Bellou et al., 2012). When compared to non-exercise control, the exercise trial significantly increased VLDL clearance and significantly reduced hepatic secretion (Bellou et al., 2012). Up to 79% of the postprandial triglyceride reduction on the day following exercise is attributable to hepatically derived large VLDL (Gill et al., 2006; Gill, Frayn, Wootton, Miller, & Hardman, 2001). Together, results from Bellou et al. (Bellou et al., 2012) and Al-Shayji et al, (Al-Shayji et al., 2012), indicate that the reduction in triglycerides in the hours following exercise is due to decreases in VLDL production and increases in VLDL clearance.

The ability of exercise to increase glucose uptake and improve insulin sensitivity may play a role in reducing hepatic VLDL production (King et al., 1995). During exercise glucose uptake is increased in the absence of insulin (Santos, Ribeiro, Gaya, Appell, & Duarte, 2008). Exercise reduces insulin concentration in the postprandial period: exercise at 60% of VO_2max 12 hours before an oral fat tolerance test lowers postprandial insulin concentration significantly when compared to non-exercise control and exercise 24 hours before a meal (Gill & Hardman, 2000; Zhang et al., 2004). In obese men, high-intensity exercise, e.g. 85% of VO_2max to exhaustion, performed 12 hours before a euglycemic hyperinsulinemic clamp significantly increases glucose disposal (Devlin & Horton, 1985). LPL activity in skeletal muscle is decreased under conditions of elevated insulin concentration and therefore the lower insulin concentrations observed following exercise may allow for enhanced LPL activity and subsequent triglyceride hydrolysis (Kiens et al., 1989). In middle-aged overweight subjects, insulin resistance, estimated by the Homeostatic Model Assessment (HOMA-IR), is significantly correlated with large VLDL production rate (Gill et al., 2004). The effect of exercise in increasing insulin sensitivity and glucose disposal may permit improvements in hyperglycemia in subjects with metabolic disease. Reduced glucose delivery to the liver would lessen substrate availability for VLDL assembly, and subsequently could reduce hepatic VLDL production (Wu et al., 2010).

Hurren, Balanos, and Blannin (Hurren, Balanos, & Blannin, 2011), have shown that, on the day following 90 minutes of exercise at 60% of maximal capacity, total blood flow through the femoral artery and hepatic portal vein is significantly increased during the postprandial period when compared to a non-exercise control condition. In addition to increased blood flow, a 22% lower postprandial triglyceride response was observed following exercise when compared to non-exercise control (Hurren et al., 2011). This study, conducted in sedentary overweight men, provides evidence that alterations in blood flow on the day following moderate-intensity exercise may indeed affect postprandial substrate delivery to the tissues responsible for metabolizing fatty acids.

Potential differences in postprandial lipemia following low- and high- intensity exercise may be observed due to increased EPOC energy expenditure following high-intensity exercise. Increased energy expenditure would require greater mobilization of energy stores from hepatic tissue and skeletal muscle. IMTG has been shown to be relied upon more heavily during exercise at 65 and 85% when compared to 25% of maximal capacity (Romijn et al., 1993). Although carbohydrate energy stores make a greater contribution to energy demands with increases in exercise intensity, lipid oxidation may be increased in the hours following exercise (Kuo, Fattor, Henderson, & Brooks, 2005; Romijn et al., 1993). During the 3 hours following moderate intensity exercise at 45 and 65% of VO_2peak, lipid oxidation is increased when compared to non-exercise control and pre-exercise values (Mantyselka et al., 2012). Enhanced lipid oxidation in the post-exercise period coupled with increased EPOC following high-intensity exercise, may contribute to an increased substrate deficit. The increased utilization of IMTG during exercise and lipid oxidation following exercise may be partially responsible for alterations in postprandial lipemia.

In summary, multiple factors likely contribute to improvements in postprandial lipemia following aerobic exercise. Following moderate- and high-intensity exercise skeletal muscle LPL activity is likely increased, resulting in greater ability to clear TRL (Greiwe et al., 2000; Kiens et al., 1989). In addition, hepatic VLDL output may be reduced in the hours following moderate-intensity exercise (Al-Shayji et al., 2012; Gill et al., 2006). Reductions in postprandial insulin concentration have been observed following moderate exercise, and glucose disposal has been shown to be increased following higher-intensity exercise (Devlin & Horton, 1985; Zhang et al., 2004). These factors, in combination with increased blood flow to skeletal muscle and hepatic tissue, may contribute to the beneficial effects of aerobic exercise on postprandial blood lipids (Hurren et al., 2011).

Conclusions

Atherogenic disease is the leading cause of death in United States, with the prevalence of obesity and MetS increasing (Ogden et al., 2006; Roger et al., 2011). Blood lipid changes that occur in the postprandial state promote CVD, with triglyceride-rich particles elevated following meals (Wojczynski et al., 2011; Zilversmit, 1979). Low-, moderate-, and high- intensity aerobic exercise is known to favorably alter postprandial lipids, and is a useful modality for reducing CVD risk (Freese et al., 2011; Tsetsonis & Hardman, 1996a). The energy expenditure of exercise appears to dictate alterations in postprandial lipemia (Gill et al., 1998). While multiple studies have compared low- and moderate- intensity exercise, none have directly compared low- and high- intensity exercise. Higher-intensity exercise is known to produce greater post-exercise energy expenditure (Borsheim & Bahr, 2003). The contribution of EPOC to changes in postprandial lipemia has not been determined. Because changes in postprandial lipemia have been linked to exercise energy expenditure, it is possible that increased EPOC following high-intensity exercise explains the favorable effects of exercise of greater intensity on postprandial lipemia.

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