

Sex-related differences in fuel utilization and hormonal response to exercise: implications for individuals with type 1 diabetes

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Abstract

Sex-related differences in metabolic and neuroendocrine response to exercise in individuals without diabetes have been well established. Men and women differ in fuel selection during exercise, in which women rely to a greater extent on fat oxidation, whereas males rely mostly on carbohydrate oxidation for energy production. The difference in fuel selection appears to be mediated by sex-related differences in hormonal (including catecholamines, growth hormone, and estrogen) response to different types and intensities of exercise. In general, men exhibit an amplified counter-regulatory response to exercise, with elevated levels of catecholamines compared to women. However, women exhibit greater sensitivity to the lipolytic action of the catecholamines and deplete less of their glycogen stores than men during exercise, which suggests that women may experience a greater defense in blood glucose control after exercise than men. Conversely, little is known about sex-related differences in response to exercise in individuals with type 1 diabetes (T1D). A single study investigating sex-related differences in response to moderate aerobic exercise in individuals with T1D found sex-related differences in catecholamine response and fuel selection, but changes in blood glucose were not measured. To our knowledge, there are no studies investigating sex-related differences in blood glucose responses to different types and intensities of exercise in individuals with T1D. This review summarizes sex-related differences in exercise responses that could potentially impact blood glucose levels during exercise in individuals with T1D and highlights the need for further research.

Key words: physical activity, type 1 diabetes, sex-related differences, fuel selection

Introduction

Traditionally, exercise studies have excluded women due to the potential impact of fluctuating hormones caused by the menstrual cycle. Thus, the majority of what we know regarding exercise physiology pertains mostly to men. Recently, there has been an increasing amount of studies that have sought to include both male and female participants, and sex-related differences in exercise have been more widely established. Studies comparing the neuroendocrine and metabolic responses to exercise in nondiabetic males and females have shown clear sex-related differences in fuel selection (Horton et al. 1998; Davis et al. 2000b; Galassetti et al. 2002; Mittendorfer et al. 2002; Steffensen et al. 2002; Riddell et al. 2003; Henderson et al. 2007; Tarnopolsky 2008; Fragala et al. 2011; Isacco et al. 2012; Hedrington and Davis 2015; Devries 2016; Wiecek et al. 2017) and the responses of hormones such as catecholamines (Amiel et al. 1993; Gratas-Delamarche et al. 1994; Horton et al. 1998; Davis et al. 2000b; Pullinen et al. 2002; Steffensen et al. 2002; Hedrington and Davis 2015; Justice et al. 2015), testosterone (Kraemer et al. 1998; Nindl et al. 2001; Linnamo et al. 2005; Fragala et al. 2011; Benini et al. 2015), estrogen (Horton et al. 1998; Hamadeh et al. 2005; Devries et al. 2006; Isacco et al. 2012) and growth hormone (Davis et al. 2000b; Esbjörnsson et al. 2009; Eliakim et al. 2014; Luk et al. 2015). These factors influence how women and men respond to the same exercise program, and have thus brought about the suggestion for sex-specific training protocols to enhance health and performance (Devries 2016).

While there is extensive research on exercise in individuals without diabetes, very little is known about sex-related differences in response to exercise in individuals with type 1 diabetes (T1D). Most studies on exercise in T1D are performed on men (Wahrenberg et al. 1989; Purdon et al. 1993; Ramires et al. 1993; Raguso et al. 1995; Bussau et al. 2007; Chokkalingam et al. 2007; Jenni et al. 2008; Maran et al. 2010; Benbenek-Klupa et al. 2015; Campbell et al. 2015a; Moser et al. 2015; Bally et al. 2016), and those that include both men and women fail to recognize the potential sex-related differences in neuroendocrine and metabolic responses to exercise (Zinman et al. 1977; Hubinger et al. 1985; McGregor et al. 2002; Guelfi et al. 2005; Robitaille et al. 2007; Arutchelvam et al. 2009; Iscoe and Riddell 2011; Adolfsson et al. 2012; Dube et al. 2013; Yardley et al. 2013; Yardley et al. 2014; Campbell et al. 2015b; Yardley et al.

2015). These differences have the potential to greatly impact the counter-regulatory response to exercise, possibly resulting in differing abilities between the sexes to maintain blood glucose homeostasis (Galassetti et al. 2002). Thus, sex-related differences are an important factor to take into consideration when assessing the risk of hypoglycemia both during and after exercise in T1D. This review summarizes current knowledge on the topic of sex-related differences in exercise responses in nondiabetic individuals that may be relevant when considering the risk of hypoglycemia in individuals with T1D. Understanding sex-related differences in exercise for T1D could assist in creating sex-specific exercise guidelines to reduce the risk of hypoglycemia during and after exercise.

Methods

A narrative review approach was used to investigate the current literature on sex-related differences in exercise in individuals with and without T1D. We searched the following databases for the period January 1977 to October 2017: PubMed, MEDLINE, EMBASE, Sport Discus, and Google Scholar.

We used the following key words for the search: sex-related differences, sexual dimorphism, sex differences, exercise, physical activity, resistance exercise, high-intensity exercise, moderate exercise, aerobic exercise, anaerobic exercise, endurance exercise, fuel selection, fuel utilization, hormonal response, diabetes, type 1 diabetes, IDDM, glucose, blood glucose, glycemia, hypoglycemia, nocturnal hypoglycemia, glycogen depletion, catecholamine, growth hormone, IGF-1, insulin, glucagon, estrogen, menstrual cycle, menstrual cycle phase, follicular phase, luteal phase, and counter-regulatory response. All searches were limited to humans.

Studies were retained if they examined the effect of an acute bout of exercise on fuel utilization or hormonal response in men, women, or both sexes in individuals with and without type 1 diabetes. No study was excluded due to study design (e.g., laboratory-based studies, review articles, systematic reviews...etc.). Studies were excluded if they did not report on fuel selection, blood glucose or counter-regulatory hormones such as insulin, glucagon, epinephrine, norepinephrine, growth hormone and IGF-1, or if they were not available in the English language.

Discussion

Fuel Selection

Individuals without Diabetes

There are marked sex-related differences in fuel selection during exercise in nondiabetic individuals. Although there is no apparent difference between sexes in fuel selection in the resting state (Tremblay et al. 2010; Sarafian et al. 2016), it has been widely accepted that during exercise females exhibit a lower respiratory exchange ratio (RER), thus relying to a greater extent on fat oxidation whereas men rely mostly on carbohydrate oxidation for energy production (Horton et al. 1998; Davis et al. 2000b; Carter et al. 2001; Galassetti et al. 2002; Mittendorfer et al. 2002; Steffensen et al. 2002; Riddell et al. 2003; Henderson et al. 2007; Tarnopolsky et al. 1990; Fragala et al. 2011; Isacco et al. 2012; Hedrington and Davis 2015; Devries 2016; Wiecek et al. 2017). This trend has been established for nondiabetic males and females during aerobic exercise (Horton et al. 1998; Davis et al. 2000b; Carter et al. 2001; Mittendorfer et al. 2002; Riddell et al. 2003; Tarnopolsky et al. 1990; Isacco et al. 2012; Henderson 2014; Hedrington and Davis 2015; Devries 2016; Wiecek et al. 2017), high intensity exercise (Isacco et al. 2012) and resistance exercise (Fragala et al. 2011; Sarafian et al. 2016). Additionally, men demonstrate an earlier shift to using carbohydrates as the dominant fuel source compared to women, particularly during high intensity exercise (Venables et al. 2005).

While there are conflicting reports, the majority of studies show that a lower reliance on carbohydrate oxidation during exercise by women is related to less depletion of hepatic and muscle glycogen (Horton et al. 1998; Esbjörnsson-Liljedahl et al. 1999; Devries et al. 2006; Isacco et al. 2012). This tendency appears to be related to type and intensity of the exercise performed and/or the phase of the menstrual cycle in which the exercise is performed. Studies reporting no difference in glycogen depletion between sexes involved submaximal exercise (Table 1) on a cycle ergometer in the follicular phase of the menstrual cycle (Roepstorff et al. 2002; Zehnder et al. 2005). Investigating the relationship between phase of the menstrual cycle and glycogen depletion, Devries et al. (2006) found that submaximal exercise performed on a cycle ergometer by women in the luteal phase of the menstrual cycle, as opposed to the

follicular phase, resulted in less depletion of glycogen stores compared with men. Additionally, during higher intensity exercise such as sprints (Esbjörnsson-Liljedahl et al. 1999), running (Tarnopolsky et al. 1990), or during long duration endurance exercise (Horton et al. 1998), males appear to deplete a greater portion of their glycogen stores than females (Table 2). The type of muscle fibers recruited during exercise may also play a role: a study by Esbjörnsson-Liljedahl et al. (1999) comparing the metabolic responses to a 30-s sprint exercise in males and females, matched for age and activity level, showed that the exercise-induced muscle glycogen reduction was significantly smaller in women than in men in type I, but not type II fibers.

Lipid metabolism appears to be greater in females than in males in adipose tissue, and potentially working skeletal muscle. During exercise, women exhibit higher glycerol release from adipose tissue compared to men (Davis et al. 2000b; Carter et al. 2001; Mittendorfer et al. 2002; Steffensen et al. 2002; Hedrington and Davis 2015). In working skeletal muscle, it has been contested whether women use more intramyocellular lipids (IMCL) during exercise than men. It is known that women have greater IMCL stores than men (Devries 2016), and the majority of studies show that females use more IMCL during exercise than males (Roepstorff et al. 2002; Steffensen et al. 2002). Two studies conducted on recreationally active individuals without diabetes performing submaximal exercise at 60% VO_2max on a cycle ergometer resulted in oxidation of IMCL in females, but not in males (Roepstorff et al. 2002; Steffensen et al. 2002). However, some studies have found equal (Devries et al. 2007) or lesser (Zehnder et al. 2005) use of IMCL during exercise in females. Despite this, women have exhibited a greater percentage of IMCL in contact with mitochondria after exercise than men, which indicates the greater capacity for women to oxidize IMCL during exercise (Devries 2016).

The sex-related difference in fuel selection disappears when a carbohydrate load precedes exercise (Riddell et al. 2003; Leelayuwat et al. 2005; Wallis et al. 2006), which may be of particular relevance to individuals with T1D who often consume carbohydrates prior to exercise. Almost all studies showing sex-related differences in fuel selection occurred during exercise in the fasted state (Horton et al. 1998; Davis et al. 2000b; Carter et al. 2001; Mittendorfer et al. 2002). Studies on males and females in the

postprandial state showed similar substrate oxidation and other metabolic responses between sexes during submaximal exercise on a cycle ergometer, when subjects were infused with glucose for 60 minutes (Leelayuwat et al. 2005) or ingested a glucose solution (Wallis et al. 2006) preceding exercise. Carbohydrate intake largely eliminated sex-related differences in whole-body substrate oxidation. Riddell et al. (2003) also found this to be true in endurance exercise, in which there was a greater reliance on exogenous carbohydrates in women compared to men after 90 minutes of exercise on a cycle ergometer at 60% VO_2max . This ability for women to spare endogenous fuel sources compared to men may assist women in maintaining better blood glucose homeostasis during exercise.

Implications for type 1 diabetes

Similar sex-related differences with respect to fuel selection have been observed in individuals with T1D during moderate aerobic exercise (Galassetti et al. 2002), where women showed attenuated catecholamine responses and greater use of lipids as a fuel source. The study in question, however, used a euglycemic clamp, thereby precluding the possibility of assessing changes in blood glucose. If sex-related differences do exist in blood glucose responses to exercise in T1D, it is likely that men will have a greater risk of post-exercise hypoglycemia: due to the fact that men rely more on their glycogen stores during exercise than women a greater uptake of plasma glucose will be needed to replenish depleted glycogen stores in the recovery period (Devries et al. 2006; Yardley et al. 2013). Conversely, where women are better able to conserve glycogen stores, there will be less need for a large uptake of plasma glucose in the recovery period (Horton et al. 1998; Esbjörnsson-Liljedahl et al. 1999; Devries et al. 2006; Isacco et al. 2012). Women without diabetes have displayed a more precise defense of homeostasis in the post-exercise recovery period, including the control of fuel selection and blood glucose concentration (Henderson et al. 2008; Henderson 2014). Due to their greater capacity for lipid oxidation during exercise, women are able to regain control over glycemia and glucose flux in recovery more quickly than men (Henderson et al. 2008). As a result, men often show an elevated rate of lipid mobilization post-exercise compared to women, in attempt to preserve glucose concentrations when restoring glycogen stores depleted from exercise (Horton et al. 1998; Henderson et al. 2007).

Catecholamines

Individuals without Diabetes

There is an evident sex-related difference in catecholamine response to various types and intensities of exercise. While there are studies that report no sex-related differences in catecholamine response to a Wingate test (30-s maximum sprint on a cycle ergometer) in recreationally active individuals (Vincent et al. 2004), and to 14 minutes of anaerobic exercise to exhaustion in moderately trained individuals (Marliss et al. 2000), the majority of studies report a significantly greater catecholamine response to various types of exercise in males compared to females (Amiel et al. 1993; Gratas-Delamarche et al. 1994; Horton et al. 1998; Davis et al. 2000b; Pullinen et al. 2002; Steffensen et al. 2002; Hedrington and Davis 2015; Justice et al. 2015). Davis et al. (2000b) matched men and women for age, BMI, fitness level and fat mass and found significantly elevated epinephrine and norepinephrine concentrations in men compared to women during moderate aerobic exercise on a cycle ergometer in the fasted state (Davis et al. 2000b). The same results were found in a similar study on participants in the postprandial state, in which men had significantly higher epinephrine levels compared to women during moderate aerobic exercise on a cycle ergometer (Steffensen et al. 2002). Horton et al. (1998) compared the metabolic effects of endurance exercise on a cycle ergometer for 2h at 40% VO_2max in men and women, which showed that long duration aerobic exercise also produces significantly greater epinephrine and norepinephrine levels in men than in women (Horton et al. 1998). High intensity and resistance exercise (Table 3), which elicit substantially higher levels of catecholamines compared to aerobic exercise, also display the same sex-related differences as moderate intensity and endurance exercise (Pullinen et al. 2002; Justice et al. 2015).

While men have exhibited an elevated catecholamine response to exercise compared to women, there is an apparent sex-related difference in sensitivity of lipolytic activity to catecholamines during exercise. Catecholamines increase lipolysis during exercise, and thus higher lipolytic rates in males would be expected compared to females, due to their higher catecholamine response (Horton et al. 1998; Hedrington and Davis 2015). However, an endurance exercise study consisting of 2h of cycling at 40%

VO₂max found that there was no difference between the sexes in circulating levels of glycerol, an indicator of whole body lipolysis, despite an elevated catecholamine response in men (Horton et al. 1998). Further studies observed the same phenomenon (Steffensen et al. 2002; Isacco et al. 2012; Hedrington and Davis 2015), and thus elevated levels of lipolysis in women despite lower levels of catecholamines than men imply a greater sensitivity to the lipolytic action of the catecholamines in women. It is suggested that women have a higher β -adrenergic sensitivity, which would stimulate lipolysis, and decreased α -adrenergic sensitivity, which would inhibit lipolysis, compared to men (Steffensen et al. 2002; Isacco et al. 2012; Schmidt et al. 2014; Hedrington and Davis 2015). While both α -adrenergic and β -adrenergic receptors are activated in men to a relatively equal extent during exercise, women have a greater sensitivity to β -adrenergic receptors, resulting in greater net lipolysis (Hedrington and Davis 2015). To examine this, Schmidt et al. (2014) investigated the sex-related differences in the relative contribution of specific adrenergic receptors in metabolic responses. Epinephrine infusion resulted in greater lipolytic responses in women compared to men, leading to the conclusion that there was lower activation of the α -adrenergic receptors in women (Schmidt et al. 2014). Thus, during exercise when epinephrine is elevated, women have relatively greater lipolysis and fat oxidation than men.

Implications for type 1 diabetes

Individuals with T1D appear to display the same sex-related differences in catecholamine response to exercise as nondiabetic individuals. Galassetti et al. (2002) found that after 90 minutes of aerobic exercise on a cycle ergometer at 50% VO₂max, epinephrine and norepinephrine responses to exercise were greater in men compared to women with T1D (Galassetti et al. 2002). However, the elevated catecholamine response in men was not paralleled by a higher lipolytic rate (Galassetti et al. 2002). In fact, lipolytic responses and circulating glycerol were higher in women compared to men during exercise. This may indicate that women with T1D display the same greater sensitivity to β -adrenergic effects and diminished activation of α -adrenergic receptors as do nondiabetic females (Galassetti et al. 2002). Whether this results in sex-related differences in blood glucose changes during and after exercise is unknown, as the study in question used a euglycemic clamp, and was thus unable to measure changes

in blood glucose. Galassetti et al. (2002) did, however, find that despite the sex-related differences in catecholamine response in T1D individuals, there was no difference in endogenous glucose production or the need for exogenous glucose. Further research is needed to determine the effect this would have on blood glucose changes and the risk of hypoglycemia during and after exercise in individuals with T1D.

Estrogen

Individuals without Diabetes

The female sex hormone, estrogen, is a contributing factor in influencing fuel selection during exercise in men and women. Estrogen, specifically 17β -estradiol, promotes lipid oxidation and decreases carbohydrate oxidation during exercise (Horton et al. 1998; Hamadeh et al. 2005; Devries et al. 2006; Isacco et al. 2012). In a study aimed to determine the effect of 17β -estradiol supplementation on glucose kinetics and substrate use, Devries et al. (2005) recruited recreationally active young men to receive either placebo or 17β -estradiol orally for eight days. Following this supplementation, participants exercised for 90 min on a cycle ergometer at 65% VO_2 max. Compared to the control placebo group, men supplemented with 17β -estradiol had a lower RER and therefore less carbohydrate oxidation, with significantly higher lipid oxidation (Devries et al. 2005). A similar study by Hamadeh et al. (2005) had parallel results, with estrogen supplementation resulting in a shift in whole body RER, carbohydrate and lipid oxidation towards the patterns found in women (Hamadeh et al. 2005).

Different phases of the menstrual cycle can also influence metabolism during exercise. Due to fluctuating hormone levels, women display differing metabolic responses to exercise depending on the phase of the menstrual cycle in which they were tested. Most studies test women in the early follicular phase, as during this phase of the menstrual cycle estrogen concentrations are relatively stable and do not differ markedly between men and women (Fragala et al. 2011). This limits the influence that estrogen could have on fuel selection during exercise. During the luteal phase of the menstrual cycle, there is a higher level of circulating estrogen and thus a higher relative rate of fat oxidation in females during exercise (Riddell et al. 2003). Devries et al. (2006) investigated the effects that different concentrations of estrogen and progesterone during the luteal and follicular phases of the menstrual cycle have on fuel

selection during exercise. Recreationally active young women and men underwent 90 min of exercise on a cycle ergometer at 65% VO_2max . The female participants were split into two groups, with half testing in the follicular phase and half in the luteal phase. Results showed that women in the luteal phase had lower glucose appearance and disappearance rates as well as glycogen use than women testing in the follicular phase (Devries et al. 2006). In addition, both groups of females displayed a lower RER than men during exercise, indicating a greater reliance on lipids as a fuel source.

While circulating levels of estrogen do not differ significantly between the sexes during the follicular phase of the menstrual cycle, women often experience an elevation in circulating estradiol following an acute bout of exercise, whereas men do not (Consitt et al. 2002; Fragala et al. 2011). This has occurred in studies involving resistance exercise (Kraemer et al. 1995; Copeland et al. 2002) and aerobic exercise (Jurkowski et al. 1978; Copeland et al. 2002) in both the luteal (Jurkowski et al. 1978; Kraemer et al. 1995; Copeland et al. 2002) and follicular phase (Jurkowski et al. 1978; Kraemer et al. 1995) of the menstrual cycle. The magnitude of increase in estradiol to an acute bout of exercise is also significantly greater in the luteal phase compared to the follicular phase (Jurkowski et al. 1978; Kraemer et al. 1995; Consitt et al. 2002). This exercise-induced increase in estradiol can result in a greater contribution of fat oxidation to energy production during exercise in females compared to males.

Though it is apparent that levels of estrogen can affect metabolism during exercise, estrogen does not appear to be the sole determinant for fuel selection in females. Numao et al. (2009) compared substrate oxidation during moderate-intensity aerobic exercise in obese men and postmenopausal obese women. At rest and during exercise, there was no significant difference between the sexes in concentrations of 17β -estradiol. Despite this, RER was still lower in women than in men during exercise, indicating a higher rate of lipolysis. These results suggest that an elevated level of lipolysis in women does not depend solely on higher levels of 17β -estradiol.

Implications for type 1 diabetes

Higher estrogen levels in women with T1D compared to men with T1D could offer a mechanism for control over glucose homeostasis during exercise. The enhanced lipolytic rate and attenuated

carbohydrate oxidation associated with elevated estrogen levels might be a means for conserving plasma glucose and glycogen stores, thus resulting in less risk of hypoglycemia, particularly post-exercise when stores are being replenished (Devries et al. 2006; Yardley et al. 2013). Furthermore, the phase of the menstrual cycle could influence blood glucose control during exercise. Studies have shown that women exercising in the luteal phase (which is associated with higher levels of estrogen) compared to the follicular phase of the menstrual cycle experienced less glycogen depletion (Devries et al. 2006), higher lipid and lower carbohydrate oxidation (Isacco et al. 2012) and greater concentrations of blood glucose (Zderic et al. 2001). While it has not been studied in individuals with T1D, exercising in the luteal phase could offer a greater defense against hypoglycemia during and after exercise for women with T1D. Further research is needed to investigate the effects that estrogen levels and phases of the menstrual cycle have on blood glucose control during exercise in individuals with T1D to determine their impact on exercise-induced hypoglycemia.

Growth Hormone

Individuals without Diabetes

There is a lack of consensus regarding sex-related differences in growth hormone response to exercise. Some studies report a significantly higher growth hormone response in men compared to women after sprint (Justice et al. 2015), aerobic exercise (Vislocky et al. 2008; Tarnopolsky et al. 1990; Henderson et al. 2007) or resistance exercise (Linnamo et al. 2005), while others report a greater growth hormone response in women after resistance exercise (Luk et al. 2015) or sprints (Eliakim et al. 2014). The majority of studies, however, report a similar response in males and females in which both sexes experience a similar relative increase in growth hormone levels during and following exercise that lasts longer than 10 minutes (Kraemer et al. 1991; Davis et al. 2000b; Consitt et al. 2002; Esbjörnsson et al. 2009; Benini et al. 2015, Pullinen et al. 2002).

Despite the similar absolute increase in growth hormone levels that most studies report, males and females exhibit a different pattern of growth hormone release during exercise. Studies report higher growth hormone peaks in women, that appear sooner and return to baseline more quickly (Davis et al.

2000b; Esbjörnsson et al. 2009) while men sustain a more prolonged response (Davis et al. 2000b; Esbjörnsson et al. 2009; Eliakim et al. 2014; Luk et al. 2015). These sex-related differences in growth hormone response can be attributed to a lack of testosterone response in women (Consitt et al. 2002). Women experience little or no increase in testosterone levels in response to exercise (Kraemer et al. 1991; Enea et al. 2011; Fragala et al. 2011), thus growth hormone appears to compensate for the anabolic requirements stimulated by acute exercise (Kraemer et al. 1993; Fragala et al. 2011). Furthermore, women have a higher resting basal level of growth hormone than men (Kraemer et al. 1998; Wideman et al. 1999; Consitt et al. 2002), particularly in the early follicular phase of the menstrual cycle (Kraemer et al. 1991). Since most exercise studies are performed on women during the early follicular phase of the menstrual cycle (due to low levels of estrogen in this phase), there are marked sex-related differences in basal growth hormone levels (Fragala et al. 2011), and subsequently often higher peaks of growth hormone in women during exercise (Davis et al. 2000b; Esbjörnsson et al. 2009; Luk et al. 2015). Additionally, estrogen is known to release a growth hormone stimulating factor (Consitt et al. 2002), and thus elevated levels of circulating estrogen are associated with higher growth hormone concentrations (Luk et al. 2015).

When examining growth hormone response to exercise, it is important to take into consideration insulin-like growth factor-1 (IGF-1), a hormone similar in structure to insulin that mediates many actions of growth hormone (Kraemer et al. 1991). The growth hormone-insulin-like growth factor-1 (GH-IGF-1) axis primarily regulates fundamental growth, development, metabolic and reparative processes, but has also been suggested to mediate many of the anabolic effects associated with aerobic, anaerobic and resistance exercise (Eliakim et al. 2014). Growth hormone and IGF-1 have a bi-directional relationship, in which growth hormone stimulates IGF-1, and IGF-1 feedback inhibits growth hormone (Frystyk 2004). However, during exercise, IGF-1 levels appear to be independent of growth hormone responses (Consitt et al. 2002). There has been inconsistency in reports of IGF-1 response to exercise, with studies showing increases, decreases, and no changes in circulating total IGF-1 (Gatti et al. 2012). It appears that IGF-1 response to exercise depends on type, intensity and duration of exercise, with most studies reporting a

significant increase in IGF-1 using a high-intensity constant-power exercise stimulus (Copeland and Heggie 2008).

It is contested whether sex-related differences exist in IGF-1 response to exercise. One study found that in response to an acute bout of high-intensity anaerobic exercise, there was a significant increase in IGF-1 in males but not females, however, there were no significant between-sex effects (Eliakim et al. 2014). Other studies have found no differences between sexes in response to 10 minutes of high-intensity cycling, with short term elevations in IGF-1 in both males and females (Bang et al. 1990; Cappon et al. 1994). The increase in IGF-1 in response to 10 minutes of high-intensity cycling also does not appear to depend on the phase of the menstrual cycle that females are tested in (Hornum et al. 1997). Additionally, a study investigating IGF-1 response to ultra-endurance exercise found no sex-related differences between males and females, with slight decreases in IGF-1 levels occurring similarly in both males and females (Berg et al. 2008).

The marked sex-related difference in growth hormone response to exercise can influence blood glucose control in males and females. Increases in growth hormone stimulate lipolysis and lipid oxidation, suppressing glucose oxidation and consequently increasing plasma glucose levels (Kraemer et al. 1991). Thus, higher resting levels of growth hormone in women due to higher levels of estrogen may preserve plasma glucose levels to a greater extent in women than in men. In terms of IGF-1 and glucose response, studies have shown that treatment of IGF-1 lowers plasma glucose in subjects with and without T1D, however, it is unclear to what extent endogenous IGF-1 participates in glucose homeostasis (Frystyk 2004).

Implications for type 1 diabetes

Although studies are limited, individuals with T1D do not appear to display the same sex-related differences in growth hormone response to exercise as nondiabetic males and females. In individuals with T1D, Galassetti et al. (2002) found that the growth hormone response was significantly lower in women compared to men following an acute bout of submaximal exercise (Galassetti et al. 2002). However, women still exhibited a greater lipolytic response, suggesting the possibility of greater tissue sensitivity to

growth hormone in women than in men. It remains unknown why women with T1D appear to produce a lower growth hormone response to exercise than nondiabetic women, and further studies are needed to investigate this phenomenon.

Individuals with T1D have impairment of the GH-IGF-1 axis, characterized by exaggerated exercise-induced growth hormone and lower IGF-1 levels, as a consequence of insulin deficiency, compared to the general population (Palta et al. 2014; Jenni et al. 2010; Frystyk 2004; Tonoli et al. 2014). A study investigating the effects of an acute bout of high intensity exercise on a cycle ergometer found that at all time points, individuals with T1D has significantly lower IGF-1 levels than individuals without T1D (Tonoli et al. 2014). However, this study found that T1D does not influence the IGF-1 response to acute high-intensity exercise, with comparable increasing effects on IGF-1 found in T1D and non-T1D.

It is unknown whether sex-related differences exist in IGF-1 response to exercise in individuals with T1D. If they did, this could have important implications for blood glucose levels. IGF-1 is necessary for normal insulin sensitivity; it binds to insulin receptors to stimulate glucose transport while simultaneously inhibiting glucose release from the liver and lowering blood glucose levels (Tonoli et al. 2014). Thus, decreased IGF-1 levels could diminish the homeostasis of glucose metabolism. As mentioned, however, it is unknown to what extent endogenous IGF-1 affects blood glucose levels (Frystyk 2004) and whether or not sex-related differences exist. Further elucidation is therefore required.

Insulin Sensitivity

Individuals without Diabetes

It has been contested whether or not there are sex-related differences in insulin sensitivity in response to exercise. Some studies have found that men and women experience a similar improvement of insulin sensitivity in response to an acute bout of exercise on a cycle ergometer for 90 minutes at 80% of anaerobic threshold (Davis et al. 2000b) or for 60 minutes at 50% VO_2 max after either receiving a glucose infusion or an oral ingestion of a high-carbohydrate meal (Leelayuwat et al. 2005). Conversely, other studies have found that women experience a greater improvement of insulin sensitivity in response to 90 minutes of submaximal exercise on a cycle ergometer at 86% of lactate threshold under a

hyperinsulinemic-euglycemic clamp (Perreault et al. 2004), or to 30 minutes of cycling exercise at 60% VO_2max following an oral ingestion of a glucose solution (Boisseau et al. 2000). Furthermore, the phase of the menstrual cycle that women are tested in may also have an impact on insulin sensitivity during exercise. Studies by Pulido and Salazar (1999) and Valdes and Elkind-Hirsch (1991) found that there was a significant decrease in insulin sensitivity in women during the luteal phase of the menstrual cycle compared to the follicular phase, though this was not tested under exercise conditions.

Implications for type 1 diabetes

Sex-related differences in insulin sensitivity in individuals with T1D in response to exercise are unknown. If they existed, differences in insulin sensitivity could result in differing abilities to maintain blood glucose levels during exercise. Increases in insulin sensitivity are related to an increased risk of post-exercise hypoglycemia in individuals with T1D (Jimenez et al. 2009). Furthermore, depletion of skeletal muscle glycogen stores is positively correlated with exercise intensity (Hougham and Ross 2011), and exercise intensity has been associated with improved insulin sensitivity (Black et al. 2010; Hougham and Ross 2011). Because most studies have shown a greater glycogen depletion in men (Horton et al. 1998; Esbjörnsson-Liljedahl et al. 1999; Devries et al. 2006; Isacco et al. 2012), this may result in a higher insulin sensitivity in men. Thus, men, especially those of higher fitness levels, might have a greater risk of experiencing hypoglycemia during and after exercise than women. Additionally, similar to women without diabetes, women with T1D experience decreased insulin sensitivity during the luteal phase of the menstrual cycle compared to the follicular phase, resulting in an increased risk of hyperglycemia during this phase (Brown et al. 2015). However, the impact this would have on blood glucose levels during exercise is unknown, and further studies are warranted to investigate the potential implications. It is also important to note that while insulin sensitivity plays a role in blood glucose control during and after exercise, this role is minor compared to the levels of circulating exogenous insulin in individuals with T1D. The risk of hypoglycemia as a result of exercise-induced insulin sensitivity is greatly diminished by the reduction of basal insulin before exercise (Thabit and Leelarathna 2016) in individuals with T1D.

Glucagon

Individuals without Diabetes

There are conflicting reports regarding glucagon response to exercise in nondiabetic men and women. A study by Davis et al. (2000b) reported a similar increase in plasma glucagon in both sexes following 90 minutes of continuous submaximal exercise on a cycle ergometer at 80% of anaerobic threshold (Davis et al. 2000b). Similar results were also reported in a study by Justice et al. (2015), in which, after repeated bouts of high intensity sprints, there was no main effect of sex on changes in plasma glucagon concentrations (Justice et al. 2015). However, other studies have reported a lower glucagon response to exercise in females compared to males exercising on a cycle ergometer at ~50% VO_2max (Perreault et al. 2004; Horton et al. 2006a; Tarnopolsky et al. 1990; Henderson et al. 2008). Nevertheless, in all studies, despite some differences reported in magnitude, both males and females showed an increase in glucagon production in response to exercise.

Implications for type 1 diabetes

Type 1 diabetes is associated with β -cell death that is accompanied by a loss of α -cell function over time (Banarer et al. 2002), thus impairing the counter-regulatory responses to episodes of stress, including glucagon response to hypoglycemia (Davis et al. 2000a; Galassetti et al. 2002). The impaired glucagon response appears to happen evenly between the sexes, with no reported sex-related differences in glucagon response to exercise in T1D. Galassetti et al. (2002) investigated the metabolic responses to submaximal exercise in individuals with T1D and found that both males and females experienced similar increases in glucagon. Thus, glucagon does not appear to contribute to sex-related differences in blood glucose control during exercise in individuals with T1D.

Conclusion

There are well known sex-related differences in exercise in individuals without diabetes. Females display a lower RER during exercise, relying to a greater extent on lipid oxidation whereas males rely more on carbohydrate oxidation. This could be the result of higher concentrations of estrogen in females, which promotes lipid oxidation and glycogen sparing, as well as a greater sensitivity to the lipolytic action of catecholamines. Furthermore, elevated resting levels of growth hormone and greater peaks in

growth hormone response to exercise in women could be a contributing factor to the sex-related differences in fuel utilization.

Sex-related differences in response to different types of exercise in individuals with T1D remain unclear. While knowledge is limited, a single study investigating the sex-related differences in submaximal exercise in individuals with T1D has paralleled the sex-related differences found in individuals without diabetes with respect to fuel selection and catecholamine response (Galassetti et al. 2002). However, this study used a euglycemic clamp to maintain blood glucose levels during exercise, and thus blood glucose responses to exercise were not measured. Furthermore, one study is not enough to draw conclusions on sex-related differences in exercise in T1D.

Overall, we do not know whether there are significant differences between men and women with T1D in response to different types and intensities of exercise, and whether this would influence blood glucose control. We can only speculate based on limited evidence that individuals with T1D would display the same sex-related differences as nondiabetic males and females, and that these might impact blood glucose responses to exercise. Further research is needed to investigate these possible sex-related differences in T1D, as this could have important implications for the development of sex-specific insulin adjustment and carbohydrate intake guidelines for the prevention of hypoglycemia during and after exercise.

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Table 1. Summary of studies on sex-related differences in aerobic exercise.

Study	Design		Change during exercise									
	Participants		Exercise		Intensity	Prandial State	Fuel Selection	Catecholamine	Growth Hormone	Estrogen	Glucagon	Blood Glucose
Riddell et al. (2003)	7/7	ET	Cycle	90 min	60% VO ₂ max	CHO load	Higher RER in males	--	--	--	--	Similar levels
Horton et al. (1998)	14/14	T/UT	Cycle	120 min	40% VO ₂ max	Fasted	Higher RER in males	Greater increase of E and NE in males	--	Greater increase in females	--	Higher levels in males
Mittendorfer et al. (2002)	5/5	UT	Cycle	90 min	50% VO ₂ max	Fasted	Similar RER. Higher lipolytic rate in females.	Similar increase of E and NE	--	--	--	--
Davis et al. (2000b)	8/8	UT	Cycle	90 min	80% AT	Fasted	Higher CHO oxidation in males	Greater increase of E and NE in males	Similar increase	--	Similar increase	--
Henderson et al. (2007)	10/10	UT	Cycle	90 min 60 min	45% VO ₂ max 65% VO ₂ max	3 h after standard breakfast	Higher RER in males	Similar increase Greater increase of E in males	Sig. increase in males only	--	--	--
Steffensen et al. (2002)	21/21	UT/ MT/ ET	Cycle	90 min	60% VO ₂ max	Fasted	Similar RER. IMCL depletion in females only.	Greater increase of E in males. Similar NE increase.	--	Higher in females	--	--
Devries et al. (2006)	13/11	MT	Cycle	90 min	65% VO ₂ max	Fasted	Higher RER in males	--	--	Similar levels	--	Similar levels
Tremblay et al. (2010)	6/12	MT	Cycle	120 min	57% VO ₂ max	CHO load Water	Similar RER Higher RER in males	--	--	--	--	Similar levels
Roepstorff et al. (2002)	7/7	ET	Cycle	90 min	58% VO ₂ max	Fasted	Similar RER. Greater IMCL depletion in females.	Similar increase of E and NE	--	--	--	Similar levels
Zehnder et al. (2005)	9/9	ET	Cycle	180 min	50% VO ₂ max	Fasted	Similar RER. Greater IMCL depletion in males	--	--	--	--	Similar levels
Devries et al. (2007)	17/19	MT/ ET	Cycle	90 min	~63% VO ₂ max	Fasted	Higher RER in males. Similar IMCL use.	--	--	--	--	--

Note: M, male; F, female; UT, untrained; MT, moderately trained; ET, endurance trained; E, epinephrine; NE, norepinephrine; RER, respiratory exchange ratio; IMCL, intramyocellular lipids; CHO, carbohydrate; Sig, significant.

Table 1. Summary of studies on sex-related differences in aerobic exercise, continued.

Design			Change during exercise									
Study	Participants		Exercise									
	N M/F	Training Status	Type	Duration	Intensity	Prandial State	Fuel Selection	Catecholamine	Growth Hormone	Estrogen	Glucagon	Blood Glucose
Tarnopolsky et al. (1990)	6/6	MT	Run	90-101 min (15.5 km)	~65% VO ₂ max	Fasted	Higher RER and glycogen use in males.	Similar NE. Higher E in males.	Increased in males only.	--	Greater increase in males	Higher in females.
Leelayuwat et al. (2005)	7/7	UT	Cycle	60 min	50% VO ₂ max	CHO load	Similar RER.	Similar E. Lower NE in males.	--	--	--	Similar levels
Wallis et al. (2006)	8/8	MT	Cycle	120 min	~67% VO ₂ max	CHO load Water	Similar RER	--	--	--	--	Similar levels
Henderson et al. (2008)	10/8	MT	Cycle	90 min 60 min	45% VO ₂ max 65% VO ₂ max	3 h after standard breakfast	--	--	--	--	Greater increase in males	Quicker recovery in females.
Numao et al. (2009)	10/10	Obese	Cycle	40 min	50% VO ₂ max	Fasted	Higher RER in males	Higher E and NE in males	--	Similar levels	--	--
Vislocky et al. (2008)	6/6	ET	Run	75 min	70% VO ₂ max	Fasted	--	--	Increased in males only.	--	--	Increased in females only
Perreault et al. (2004)	10/10	MT	Cycle	90 min	85% lactate threshold	Fasted.	--	Similar levels	--	--	Greater increase in males	--
Boisseau et al. (2000)	10/12	MT	Cycle	30 min	60% VO ₂ max	CHO ingestion (oral)	--	Similar levels	--	--	--	Higher in males
Horton et al. (2006a)	12/10	MT	Cycle	90 min	75% of lactate threshold	Fasted	Lower CHO oxidation in females.	Similar NE. Higher E in males.	--	--	Greater increase in males.	Similar levels
Wiecek et al. (2017)	10/10	MT	Tread-mill	45 minutes	50-55% VO ₂ max	2 h after light meal	Higher lipid oxidation in females.	--	--	--	--	--
Venables et al. (2005)	157/143	UT/MT/E T	Tread-mill	--	Graded test to exhaustion	After 4-h fast	Higher CHO, lower fat oxidation in males.	--	--	--	--	--

Note: M, male; F, female; UT, untrained; MT, moderately trained; ET, endurance trained; E, epinephrine; NE, norepinephrine; RER, respiratory exchange ratio; CHO, carbohydrate.

II

Table 2. Summary of studies on sex-related differences in high-intensity anaerobic exercise.

Study	Design		Change during exercise									
	Participants		Exercise									
	N M/F	Training Status	Type	Duration	Intensity	Prandial State	Fuel Selection	Catecholamine	Growth Hormone	Estrogen	Glucagon	Blood Glucose
Justice et al. (2015)	8/7	MT	Cycle	30 sec	Maximal (Wingate)	3h 15 min after breakfast and 60 min cycle	--	Higher E and NE levels in males.	Higher levels in males.	--	Similar levels	Similar levels
Gratas-Delamarche et al. (1994)	6/6	ST	Cycle	30 sec	Maximal (Wingate)	Fasted	--	Higher E levels in males. Similar NE.	--	--	--	--
Eliakim et al. (2014)	12/16	MT	Cycle	30 sec	Maximal (Wingate)	--	--	--	Higher levels in females.	--	--	--
Esbjörnsson et al. (2009)	10/8	MT	Cycle	3 sets of 30 sec (20 min rest)	Maximal (Wingate)	Fasted	--	--	Similar levels. Earlier peak in females.	--	--	Higher in males.
Esbjörnsson-Liljedahl et al. (1999)	20/19	MT	Cycle	30 sec	Maximal (Wingate)	Fasted	Smaller glycogen depletion in females	--	--	--	--	--
Vincent et al. (2004)	8/8	MT	Cycle	30 sec	Maximal (Wingate)	1 h 30 min after standard breakfast	--	Similar levels of E and NE.	--	Increased in females	--	Higher in females
Marliss et al. (2000)	16/12	MT	Cycle	14 min	88% VO ₂ max	Fasted	Similar RER.	Similar levels of E and NE.	--	--	Similar levels	Higher in females.

Note: M, male; F, female; UT, untrained; MT, moderately trained; ST, sprint trained; E, epinephrine; NE, norepinephrine; RER, respiratory exchange ratio; CHO, carbohydrate.

III

Table 3. Summary of studies on sex-related differences in resistance exercise.

Study	Design		Change during exercise								
	Participants	Exercise	Type	Protocol	Prandial State	Fuel Selection	Catecholamine	Growth Hormone	Estrogen	Glucagon	Blood Glucose
Pullinen et al. (1999)	9/8	MT	Bilateral leg extension-flexion	4 tests separated by 3 days. Maximum number of reps at 80%, 60%, 40% or 20% of 1RM.	Not controlled for	--	Similar levels	--	--	--	--
Benini et al. (2015)	14/7	RT	Dynamic lower and upper limb exercises.	Approx. 60 min. 3 series of 8 to 10 RM of 10 exercises. 90-120 sec rest between series and exercises.	1 h after standard breakfast	--	--	Similar levels	--	--	--
Linnamo et al. (2005)	8/8	MT	Sit-ups, bench press, bilateral leg extension.	3 loading sessions: 5 sets of 10 RM (heavy), 70% load (submaximal), 40% load (explosive). 2 week recovery period between sessions.	Fasted	--	--	Greater increase in males.	--	--	--
Luk et al. (2015)	9/10	UT	Smith-squat exercise	6 sets of 10 reps with 2 min rest at 10RM	Fasted	--	--	Greater increase in females.	--	--	--
Sarafian et al. (2016)	13/13	UT	Isometric leg press	6 cycles at 5 exercise loads (+5, +10, +15, +20, and +25 kg force)	Fasted	Higher lipid and lower CHO oxidation in females.	--	--	--	--	--
Pullinen et al. (2002)	6/6	RT	Bilateral leg extension-flexion	First, 5 sets of 10 reps at 40% 1RM (40s rest). Then, 2 sets of max reps with same load (3 min rest).	3 h after standard breakfast	--	Similar NE. Higher E in males.	Similar levels	--	--	Similar levels
Kraemer et al. (1991)	8/8	MT	Heavy resistance-full body	2 conditions of 8 different resistance exercises: 1) 5 sets at 5RM; 2) 3 sets at 10 RM.	Not controlled for	--	--	Similar levels	--	--	Similar levels

Note: M, male; F, female; UT, untrained; MT, moderately trained; RT, resistance trained; E, epinephrine; NE, norepinephrine; RER, respiratory exchange ratio; CHO, carbohydrate; RM, repetition maximum; Approx, approximately.

