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Does a Family History of Type 2 Diabetes Affect Exercise Induced Improvements in Insulin Sensitivity, Metabolic Flexibility, and Myokine Expression in Mexican-American Males?

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Abstract

A family history of diabetes (FH+) is considered a risk factor for the development of insulin resistance and type 2 diabetes. However, it is not known whether exercise induced improvement in insulin sensitivity (IS) and metabolic flexibility (MF) are impacted by a FH+. **Purpose:** To determine if a FH+ limits exercise induced improvements in Insulin sensitivity, MF, body composition, and strength following an 8-week combined aerobic and resistance training intervention compared to those without a family history of diabetes (FH-). **Methods:** 19 (FH- n=9, age 21.89 ± 0.60 years, BMI 27.51 ± 1.68 kg/m^2; FH+ n=10, age 23.41 ± 0.86 years, BMI 26.64 ± 1.02 kg/m^2) sedentary, normoglycemic, Mexican-American males underwent 8-weeks of combined exercise training 3 times/week (35-min aerobic & 45-min resistance training/session). A controlled diet (55/15/30% Cho/Pro/Fat) was provided 5 days before pre/post intervention tests. Insulin sensitivity was assessed by hyperinsulinemic euglycemic clamp. MF was assessed by change in respiratory quotient (ΔRQ) at the insulin stimulated state of the clamp compared to the fasted state. Body composition was measured using DXA. Upper and lower body strength were measured by 1 repetition maximum bench press and leg strength dynamometer respectively. **Results:** Insulin sensitivity significantly improved after 8 weeks of combined exercise training in both groups (FH- 2.99 ± 0.27 to 3.89 ± 0.28 ml/kg estimated metabolic body size (EMBS), p=0.02; FH+ 3.63 ± 0.50 to 4.82 ± 0.51 ml/kg EMBS; p=0.002). MF did not change (FH- 0.07 ± 0.01 to 0.09 ± 0.01, p=0.71; FH+ 0.08 ± 0.01 to 0.11 ± 0.02, p=0.24). Fat free mass significantly increased in both groups (FH- 54.82 ± 2.28 to 56.52 ± 1.87 kg, p=0.02, FH+ 51.14 ± 1.58 to 53.42 ± 1.8 kg, p=0.001). Upper body strength (FH- 155.00

± 20.83 to 181.10±21.13 lb, p=0.0001; FH+ 148.50 ± 16.87 to 178.00 ± 16.75 lb, p=0.0001) and lower body strength (FH- 354.44 ± 31.97 to 416.67 ± 27.55 lb, p=0.0006; FH+ 356.00 ± 20.18 to 419.50 ± 15.99 lb, p=0.0003) significantly increased in both groups. Insulin sensitivity Improvement reported as percent (%) change were not different between groups (FH- 34.90 ± 11.00 % vs. FH+ 40.66 ± 12.19 %; p>0.05). Percent change in metabolic flexibility was not blunted by FH+ between groups at baseline (FH- 9.97 ± 2.27 % vs. FH+ 10.72 ± 1.93 %; p>0.05) or post intervention (FH- 12.73 ± 2.69 % vs. 15.81 ± 3.05 %, p>0.05) **Conclusion:** FH+ was not indicative of a lower insulin sensitivity compared to FH- in healthy young men. Additionally, FH+ is not a limiting factor for exercise induced improvements in Insulin sensitivity, MF, body composition, and strength in young normoglycemic Mexican-American men.

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Chapter 1: Introduction

Type 2 Diabetes

With prevalence rates more than doubling over the last two decades, Type 2 diabetes (T2D) has now become the 7th leading cause of death in the United States [1] T2D can be diagnosed in the clinical setting by a fasting blood glucose level above 126 mg/dl [2]. T2D accounts for 90-95% of diabetes cases with a high prevalence in those who are physically inactive, obese, have a family history of T2D (FH+) and are of old age [1]. Additionally, the prevalence of T2D is greater in certain ethnic groups such as non-Hispanic blacks (17.7% aged 18 and over) and Hispanics (16.4% aged 18 and over) compared to Caucasians (9.3% aged 18 and over) [1]. It has also been shown that Hispanics have a 51% greater risk for developing diabetes compared to non-Hispanic white adults [1]. In addition to this, it has been demonstrated that those with a FH+ have a greater risk for developing the disease, with a contribution from both genetic and environmental factors [3].

Compromised Insulin Sensitivity with Family History of Type 2 Diabetes

The prevalence of T2D has been reported to be greater in the offspring of parents with T2D, compared to non-diabetic parents [3-11] (Table 1.). (Appendix A). Table 1. depicts relevant studies that investigated the effects of FH of T2D. As shown by Perez-Fuentes et al., (2014) middle aged FH+ individuals had a lower insulin sensitivity (IS), measured through quantitative insulin sensitivity check index (QUICKI) as well as greater fasting insulin levels [12]. FH+ has been reported to have a significantly lower glucose uptake capacity during insulin stimulated conditions

(hyperinsulinemic euglycemic clamp) when compared to individuals without a family history (FH-) of T2D [13]. Martin et al., (1992), examined glucose tolerant individuals for 25 years and found that 76% of individuals, who had lower insulin sensitivity during an oral glucose tolerance test, developed T2D by the end of the 25 year follow up.

Table 1. Literature Overview- Effects of Family History of Type 2 Diabetes on Insulin Sensitivity

Study	Status	Family History	Method	Outcome	Age	Sex	Race
Petersen et al. 2004	Insulin Resistant & Insulin Sensitive	One parent or grandparent	Hyperinsulinemic-Euglycemic Clamp	↓ IS in FH+	25-29	8m/18F	NA
Perseghin et al. 1997	Normoglycemic	First-degree relative	Hyperinsulinemic euglycemic clamp	↓ IS in FH+	19-41	28M/50F	White
HeilBronn et al. 2007	Normoglycemic	First-degree relative	Hyperinsulinemic euglycemic clamp	No Difference	34-52	5M/12F	White
Arslanian et al. 2005	Normoglycemic	First-degree relative	Hyperinsulinemic euglycemic clamp	↓ IS in FH+	11-12	25M/29F	White
Groop et al. 1996	Normoglycemic	First-degree relative	Hyperinsulinemic euglycemic clamp & OGTT	↓Glucose tolerance in FH+ ↓ IS in FH+	35-65	46M/39F	Hispanic
Gulli et al. 1992	Normoglycemic	First-degree relative	Hyperinsulinemic euglycemic clamp & OGTT	No Difference in OGTT ↓ IS in FH+	34-42	3M/18F	Mexican-American
Van Haeften et al. 1998	Normoglycemic	First-degree relative	Hyperglycemic clamp & OGTT	No Difference	44-47	8M/34F	White
Haffner et al. 1997	Normoglycemic & Impaired Glucose Tolerance	First-degree relative	2-h OGTT	↓Glucose tolerance in FH+	25-65	533M/743F	Hispanics & African Americans
Ishikawa et al. 1998	Normoglycemic	First-degree relative	2-h OGTT	↓ IS in FH+	26-52	52M/36F	White
Ramachandran et al. 1997	Normoglycemic & Impaired Glucose Tolerance	First-degree relative	2-h OGTT	↓Glucose tolerance in FH+	20+	810M/936F	Indian
Warram et al. 1990	Normoglycmic	First-degree relative	2-h OGTT	↓ IS in FH+	16-60	71M/84F	NA
Osei et al. 1991	Normoglycemic	Family history of diabetes	2-h OGTT FSIVGTT	↓ IS in FH+	24-30	4M/16F	N/A
Wang et al. 2008	Normoglycemic & Impaired glucose tolerance & T2D	First-degree relative	2-h OGTT HOMA-IR	↓Glucose tolerance in FH+	31-65	183M/240F	Chinese
Ryder et al. 2003	Normoglycemic	Relatives with diabetes	HOMA-IR	↓ IS in FH+	18-68	66M/77F	Hispanic

Guerrero et al. 2005	Normoglycemic	Family history of diabetes	HOMA-IR	↓ IS in FH+	18-24	18M/30F	White
Perez-Fuentes et al. 2014	Normoglycemic	First-degree relative	QUICKI	↓ IS in FH+	18-65	602 M&F	White

2-h OGTT: 2-hour Oral Glucose Tolerance Test; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance.

Lower insulin sensitivity often precedes the development of T2D, and therefore, can serve as an “early detection” in otherwise healthy normoglycemic individuals [14]. During the clinical and scientific setting there is often a tradeoff for employing the most sensitive method for testing insulin sensitivity for the most feasible method as it is primarily determined by the number of subjects, expertise, personnel, and funding. Ryder et al., (2003) and Haffner et al., (1997) assessed insulin sensitivity through an oral glucose tolerance test and demonstrated that healthy, middle aged, Mexican-American FH+ individuals had lower insulin sensitivity when compared to FH- individuals. The gold standard hyperinsulinemic-euglycemic clamp has been employed in previous studies to assess insulin sensitivity in healthy, middle aged, Mexican/Hispanic individuals and concluded that FH+ is associated with insulin resistance [3, 13]. Although the clamp is the most sensitive method to measure insulin sensitivity, its complexity and laborious nature makes it difficult to be administered in large sample populations. Therefore, due to its practicality, the minimal model Oral Glucose Tolerance Test (OGTT) is commonly used in the clinical setting to assess insulin sensitivity. These two methodologies have demonstrated to be effective in detecting differences in insulin sensitivity across various age groups and races (Table 2). (Appendix B). Table 2. depicts the relevant studies which employed various techniques to quantify insulin sensitivity.

Table 2. Literature Overview- Effects of family history of type 2 diabetes on insulin sensitivity – sorted for Insulin Sensitivity Methodology

Author	Status	Method	Outcome FH+ vs. FH-	Age	Sex	Race
Arslanian et al. 2005	Normoglycemic	Hyperinsulinemic euglycemic clamp	↓ IS in FH+	11-12	25M/29F	White
Petersen et al. 2004	Insulin resistant & Insulin sensitive	Hyperinsulinemic euglycemic clamp	↓ IS in FH+	19-36	8M/18F	Black White
Perseghin et al. 1997	Normoglycemic	Hyperinsulinemic euglycemic clamp	↓ IS in FH+	19-41	28M/50F	Mexican
Groop et al. 1996	Normoglycemic	OGTT Hyperinsulinemic euglycemic clamp	↓Glucose tolerance in FH+ ↓ IS in FH+	35-65	46M/39F	Hispanic
Gulli et al. 1992	Normoglycemic	OGTT Hyperinsulinemic euglycemic clamp	No Difference in OGTT ↓ IS in FH+	34-42	3M/18F	Mexican-American
Van Haeften et al. 1998	Normoglycemic	OGTT & Hyperglycemic clamp	No Difference	44-47	8M/34F	White
Wang et al. 2008	Normoglycemic	2-h OGTT	↓Glucose tolerance in FH+	31-65	183M/240F	Chinese
Ishikawa et al. 1998	Normoglycemic	2-h OGTT	↓Glucose tolerance in FH+	26-52	52M/36F	White
Haffner et al. 1997	Normoglycemic	2-h OGTT	↓Glucose tolerance in FH+	25-65	533M/743F	Hispanics & African Americans
Osei et al. 1991	Normoglycemic	2-h OGTT FSIVGTT	↓ IS in FH+	24-30	4M/16F	N/A
Ryder et al. 2003	Normoglycemic	HOMA-IR	↓ IS in FH+	18-68	66M/77F	Hispanic
Guerrero et al. 2005	Normoglycemic	HOMA-IR	↓ IS in FH+	18-24	18M/30F	White
Perez-Fuentes et al. 2014	Normoglycemic	QUICKI	↓ IS in FH+	18-65	602 M&F	White

2-h OGTT: 2-hour Oral Glucose Tolerance Test; FSIVGTT: Frequently Sampled Intra-venous Glucose Tolerance Test; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; QUICKI: Quantitative Insulin Sensitivity Check Index.

Furthermore, Gulli et al., (1992), demonstrated that during a hyperglycemic clamp, the amount of glucose metabolized per unit of plasma insulin concentration was

37% lower in subjects with FH+ versus FH-. It was also demonstrated that at steady-state during a hyperglycemic clamp, plasma insulin levels of FH+ subjects were significantly elevated compared to the FH-, supporting the notion of decreased insulin sensitivity in FH+ subjects. This study showed that participants with FH- require a higher glucose infusion rate compared to FH+ individuals to achieve the same plasma glucose values [15].

Metabolic Flexibility

In addition to impaired insulin sensitivity, it has been demonstrated that FH+ also have a diminished metabolic flexibility [7, 15-19]. Metabolic flexibility is defined as the ability to switch from fat to carbohydrate oxidation in response to a meal or insulin administration [20]. It has been shown that metabolically flexible individuals predominantly oxidize fat as the main source of fuel during fasting condition and are promptly able to switch to carbohydrate oxidation in response to insulin [15]. On the other hand, metabolically inflexible individuals exhibit a lower rate of fat oxidation at rest and lack the capability of switching to carbohydrate oxidation after insulin administration [16, 18, 19, 21-25].

Moreover, as demonstrated by Gulli et al., (1995), FH+ participants relied less on fat oxidation during resting conditions compared to FH- and were not able to switch to carbohydrate oxidation to the same extent as FH- during a hyperinsulinemic-euglycemic clamp. Additionally, in regard to metabolic flexibility, Ukropcova et al., (2007) showed that FH- and FH+ individuals displayed similar metabolic flexibility during a hyperinsulinemic-euglycemic clamp. On the contrary, Groop et al., (1996) demonstrated

that FH- and FH+ subjects displayed virtually the same rates of lipid and glucose oxidation during fasted and insulin stimulated conditions. The inability to suppress lipid oxidation during insulin stimulated conditions with FH+ is an indicator of compromised metabolic flexibility [15]. Metabolic flexibility has been shown to be compromised in obese individuals by a markedly lower capacity for fat oxidation during fasted conditions [21]. In a previous study, it was reported that obese individuals have a higher 24-hour respiratory quotient (RQ), which is indicative of low fat oxidation during resting conditions. Individuals with T2D were also reported to show signs of compromised metabolic flexibility during the hyperinsulinemic-euglycemic clamp. When compared to a control group (FH-), individuals with T2D were not able to increase glucose uptake during insulin-stimulated conditions [18]. Sparks et al., (2009), suggested that metabolic inflexibility is a fundamental early component of the “dysmetabolic” syndrome and provides new insight into why some people develop diabetes and some do not. This suggests that early interventions are essential to reverse these defects to help prevent T2D and cardiovascular diseases [16].

Myokine Secretion

Myokines, which are cytokines secreted from the skeletal muscle [26], have been shown to be influenced by the contractile activity of muscle, thus linking physical activity to myokine secretory response [27]. Skeletal muscle is the largest organ in individuals with a healthy body weight and activity level and accounts for ~40% of body weight [28]. Given that skeletal muscle is now recognized as an endocrine organ, it is important to investigate the effects that are elicited by muscular contraction. Recent research has

shed light on the pro/anti-inflammatory properties of several novel myokines [29]. Myokine secretion, or low-grade systemic inflammation, has been linked to insulin sensitivity, inflammation, metabolic function, obesity and T2D [28, 30-32]. The anti-inflammatory effects of exercise have shown not only to reduce inflammation but also to improve insulin resistance. As demonstrated by King et al., (2002) a strong inverse association between systemic low-grade inflammation and level of physical activity was observed. Numerous myokines have been associated with insulin resistance, obesity, and T2D, including interleukin 6 (IL-6) [33], interleukin 15 (IL-15) [34], myostatin [35], tumor necrosis factor-alpha (TNF-α) [36], and leukemia inhibitory factor (LIF) [37].

Exercise Induced Improvements in Insulin Sensitivity and Metabolic Flexibility:

It is well established that exercise training improves insulin sensitivity. Short term exercise training studies (2 – 6 weeks) reported a significant improvement in fasting plasma glucose [38], fasting insulin [38, 39], glucose tolerance [40], and insulin sensitivity measured by the gold standard, hyperinsulinemic-euglycemic clamp [41]. These improvements have been reported in healthy sedentary individuals [42], obese individuals [43, 44], as well as individuals with T2D [38]. Similarly, long-term exercise training studies have also reported significant improvements in fasting plasma glucose [45-47], fasting insulin [48-50], glucose tolerance [45, 51], and insulin sensitivity [48, 49]. These improvements following exercise training have been reported in various populations including healthy sedentary, obese [47, 52], and population with T2D [45, 46, 51]. Moreover, lifestyle exercise interventions (1 & 2 years) that include exercise and exercise plus a controlled diet group (reducing saturated fat to 10% of energy and

increasing monounsaturated fat to 10-15% of energy intake with macronutrient proportions of ~16% protein, ~37% fat, ~47% carbohydrate) have been performed on FH+ individuals by Brekke et al., (2005) and Wing et al., (1998) [44, 50]. Both studies reported that following the 2-year intervention, the diet, exercise, and diet + exercise groups significantly improved their fasting plasma insulin compared to control groups which did not take part in exercise or diet interventions. A greater degree of improvement was evident in the diet + exercise group compared to the control group. Currently, a coherent body of literature examining exercise induced improvements in healthy, sedentary individuals, particularly for those with a family history of T2D, is not complete. Additional research that investigates the effects of exercise on insulin sensitivity, fasting glucose, and fasting insulin in healthy sedentary individuals is needed.

Training Mode

The type of exercise, whether it is aerobic, [38, 39, 43, 44, 48-50, 53, 54], resistance [38, 55, 56], or combined [38, 45-47, 51, 52, 57] have shown to be beneficial and contribute towards the prevention of T2D. Aerobic exercise interventions have demonstrated to be effective in improving insulin sensitivity [38, 41, 43, 44, 49, 54], metabolic flexibility [53], and myokine secretion [44, 46, 49, 54], in sedentary [41, 49, 53], obese [43, 54], and T2D subjects [18, 38, 54]. Additionally, resistance exercise training interventions have also been shown to effectively improve insulin sensitivity [18, 55, 58-63], metabolic flexibility [18], and myokine secretion [46]. These improvements were evident in sedentary [62], obese [58, 61], and T2D subjects [46, 55, 59, 60, 63].

Furthermore, combined exercise training interventions or the concurrent training of aerobic and resistance exercise, have shown to be an effective tool to improve insulin sensitivity [18, 38, 45, 51, 52, 64], enhance metabolic flexibility [18, 52], and improve myokine expression [46] in sedentary [64], obese [47, 52], and T2D subjects [18, 38, 45, 46, 51]. Exercise training, whether it be aerobic, resistance, or combined has been shown to be a potent tool to delay or prevent the onset of T2D by improving insulin sensitivity, metabolic flexibility, and myokine expression. Although it is well established that aerobic, resistance and combined exercise training improve insulin sensitivity, metabolic flexibility and myokine expression, the body of literature concerning of these effects on FH+ individuals is limited. Additionally, it remains unclear whether FH+ is detrimental to Mexican-Americans and if their family history of T2D is restrictive of exercise induced improvements.

Exercise Mediated Improvements in Myokine Secretion

Current research has aimed at identifying the relationship between the pancreas and skeletal muscle in response to exercise. Recent data suggests that chronic inflammation is involved in the pathogenesis of pancreatic cell death, atherosclerosis, and insulin resistance and most profoundly in T2D and cardiovascular disease [65]. According to Pedersen et al., (2017), inflammation accompanied by elevated circulating levels of cytokines are found in individuals with insulin resistance and T2D. As demonstrated by Pedersen et al., (2003), the endocrine effects of skeletal muscle derived peptides produced and secreted during skeletal muscle contraction known as myokines [66], have been shown to have beneficial effects on glucose uptake [34, 67],

glucose tolerance [68], and regulation of fat oxidation [65, 68]. Additionally, it has been demonstrated that IL-6, a myokine that promotes glucagon-like peptide-1 (GLP-1) secretion and production in intestinal L cells and pancreatic β-cells contribute to the improvement of glycemic control [69]. These increases of IL-6 and GLP-1 led to improved glucose tolerance and β-cell insulin secretion [69]. This could provide an explanation to the increase of GLP-1 levels in the blood during exercise, which may be due to skeletal muscle derived IL-6 [69]. IL-6, extensively reviewed by Pedersen et al., (2016), has been speculated to contribute to both the pro-inflammatory and anti-inflammatory effects of exercise, regulate glycogen content in skeletal muscle, and contribute to insulin sensitivity through AMP-kinase (AMPK) activation [70]. IL-6 is produced in larger amounts compared to other myokines [71]. Wallenuius et al., (2002), conducted a study using IL-6 knockout mice that demonstrated to be insulin resistant and obese. Following 18 days of IL-6 administration, body weight and abdominal fat were significantly decreased in the same IL-6 knockout mice [72].

Numerous studies have shown that myokine secretion is induced by exercise. It has been shown that circulating IL-6 can increase up to 100-fold depending on the duration of exercise and the amount of muscle engaged in exercise [66]. This increase in IL-6 has been associated with increased glucose uptake, fatty acid oxidation, and enhanced insulin secretion which further contributes to increased glucose uptake into skeletal muscle [73]. Skeletal muscle's ability to adapt to exercise by enhancing β-oxidation of fatty acids, glycogen content, and intramyocellular triglyceride hydrolysis allows trained athletes to use lipid as a substrate and rely less on glucose and muscle glycogen during exercise [74].

In addition to IL-6, another myokine of interest, interleukin-15 (IL-15), has been interconnected to body weight and insulin sensitivity which has been demonstrated to regulate metabolic diseases such as obesity and diabetes [68]. It has been demonstrated that IL-15 increases glucose transporter 4 (GLUT4) expression which, in turn, increases glucose uptake into skeletal muscle cells [29]. Moreover, incubation of muscle in IL-15 has been shown to promote GLUT4 mRNA, suggesting an increase in glucose uptake capabilities [34]. Additionally, it has been demonstrated that 30-minutes of treadmill running at 70% of age predicted maximal heart rate significantly increased circulating levels of IL-15 in healthy untrained young men [75]. A study conducted by Riechman et al., (1996), demonstrated that after 10-weeks of moderate-intensity resistance exercise training, IL-15 was significantly elevated compared to pre-exercise level. These findings remained the same following the 1st session (acute effect) to following the 30th session in week 10 of the intervention (chronic effect) [76]. Furthermore, the role of IL-15 in lipid metabolism has been investigated in transgenic mice (TG) that possess elevated levels of circulating IL-15 and have shown to have higher insulin sensitivity and increased expression of various markers associated with lipid metabolism [67]. Quinn, et al. (2013), conducted a similar study that also used TG mice with elevated levels of IL-15 and demonstrated that TG mice had a significantly greater lipid oxidation capacity compared to control mice at rest and during a run to exhaustion test [77]. Given that IL-15 holds a pivotal role in glucose and lipid metabolism, it may serve an important role in regulating metabolic diseases such as T2D and obesity [78].

Myostatin, another myokine that is downregulated during exercise has been associated with muscle growth regulation [79]. It has been shown that following 5 days of resistance training, myostatin levels decreased 44%, 24 hours after the last bout of exercise [80]. Given that myostatin has been shown to hinder hypertrophy, the downregulation of myostatin after resistance exercise is supported by increases in muscle mass [80]. A 6-month aerobic exercise training (40 – 55% peak VO_2) study conducted by Hittel et al., (2010), demonstrated that plasma myostatin concentrations post-intervention significantly decreased and strongly correlated with improvements in Insulin sensitivity [35]. Furthermore, short-term endurance training has been demonstrated to elicit a downregulation of myostain in rats; with as little as 5 days of swimming for 60-minutes per day, myostatin levels decreased in the gastrocnemius and vastus lateralis [81].

These skeletal muscle specific proteins and the effects of exercise training on myokine secretion in Mexican-American FH+ vs. FH- individuals is unclear. Establishing a clear link between myokines and their contribution to insulin sensitivity, metabolic flexibility, and inflammation will be essential to further understand potential mechanisms involved in the development of T2D. Additionally, understanding these mechanisms can lead to the identification of potential targets that can help prevent T2D through exercise prescription or through pharmacological agents.

Purpose & Specific Aims

Current research concerning contributing factors to the pathogenesis of T2D has established that certain factors such as family history of T2D, ethnicity, chronically

elevated levels of inflammation markers, body fat, and lack of exercise can all increase an individual's susceptibility to develop the disease. However, it still remains unclear whether a family history of T2D in Mexican-Americans impacts exercise mediated improvements in insulin sensitivity, metabolic flexibility, and myokine concentrations. Therefore, the primary purpose of this study was to evaluate the effects of 8 weeks of a combined exercise training intervention on insulin sensitivity, metabolic flexibility, or myokine secretion in Mexican-American males with and without a family history of T2D. Specific aims:

1. To determine if normoglycemic, otherwise healthy, Mexican-American males with a first-degree family history of T2D are more insulin resistant and metabolically inflexible compared to age and BMI, matched individuals without a family history of T2D.
2. To determine whether normoglycemic, otherwise healthy, Mexican-American males with a first-degree family history of T2D are able to achieve exercise-induced improvement in insulin sensitivity and metabolic flexibility to a similar extent after 8 weeks of combined endurance and resistance exercise training compared to those without a family history of T2D.
3. Exploratory aim: To determine whether normoglycemic, otherwise healthy, Mexican-American males with a first-degree family history of T2D have alterations in plasma profile of key myokines and cytokines at baseline, after acute bouts of aerobic and resistance exercise, and after the 8-weeks of combined exercise training.

The border region of El Paso population consists of 87% Hispanics, who have a greater risk for developing T2D compared to non-Hispanic whites. Statistically, 9.4% of Americans have been diagnosed with T2D (CDC, 2017), compared to approximately 13.8% Hispanic adults in the US (diabetes.org, 2018). Furthermore, over the course of their lifetime, over 50% of Hispanic men and women, are expected to develop T2D (CDC.gov, 2018). Locally, about one in eight adults in El Paso have been reported to have T2D (healthypasodelnorte.org, 2017). The proposed study is not only relevant to the border region of El Paso which has a high Mexican-American population of 82.2% (Census.gov, 2010), but will also help answer important questions regarding exercise induced prevention of T2D and molecular mechanisms involved in an at-risk Mexican-American population.

Chapter 2: Methods

Twenty-two normoglycemic, healthy sedentary Mexican-American males between the age of 18 and 40 years were recruited to this study and were assigned into one of two groups based on whether none of the parents (FH-, n=10) or one/both parent(s) is/are diagnosed with T2D (FH+, n=12). Self-reported non-diabetic parental status in the FH- group was confirmed in 4 of the 9 participants. Two participants from the FH+ group dropped out of the study and were excluded from the statistical analyses. A subject from FH- group was excluded from statistical analyses due to noncompliance to the exercise training sessions; Thus, providing a final group allocation of FH-, n=9 and FH+, n=10. The study protocol was approved by the University of Texas at El Paso (UTEP) institutional review board.

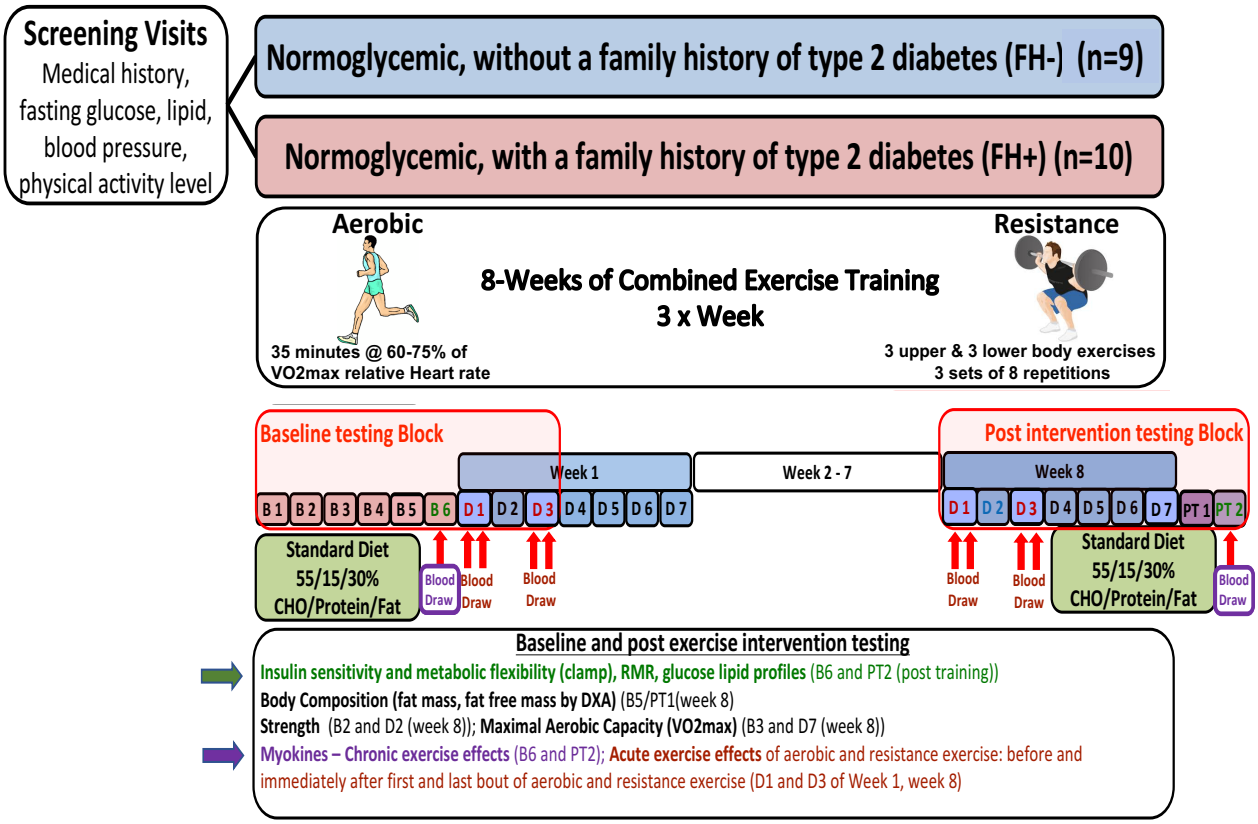

Figure 1. Study Design

Once subjects were recruited, an over the phone questionnaire was administered to determine eligibility (Appendix C). When the subject's eligibility and Mexican-American status through self-report was confirmed, a meeting was scheduled to obtain informed consent. After informed consent was obtained it was determined if subjects met any of the exclusion criterion (Table 4). If none of the exclusion criteria were met, subjects were issued an accelerometer (Table 3. S1-S7). The purpose of the accelerometer was to assess physical activity level of the participants. Less than 60 minutes spent in moderate to vigorous physical activity per week was considered sedentary [82]. If the participant met the sedentary physical activity criteria, the participant was then instructed to return for a maximal aerobic capacity (VO_2max) assessment (Table 3. B3), upper and lower body 1 repetition maximum (1RM) muscular strength (Appendix D) (Table 3. B2), body composition (Table 3. B5), and family history of disease questionnaire (Appendix E). Five days before the baseline measurement of insulin sensitivity by the gold standard hyperinsulinemic euglycemic clamp, all subjects reported any food allergies (Appendix F) and were provided with a standard diet (55% carbohydrate, 15% protein, 30% fat) (Table 3. B1-B5) to control for dietary effects on insulin sensitivity. Participants were asked to arrive at the UTEP Health Sciences building the day of the clamp after an overnight fast for assessment of insulin sensitivity and metabolic flexibility using the hyperinsulinemic euglycemic clamp (Table 3. B6). Indirect calorimetry was used to assess resting metabolic rate and metabolic flexibility before and after insulin stimulated conditions during the clamp. Fasting blood samples were collected to determine complete metabolic panel, thyroid function, lipid profile, insulin, and myokine concentrations (Table 3. B6).

Table 3. Schedule

	Screening		Baseline						Exercise Training												Post Training	
									W1	W2	W3	W4	W5	W6	W7	Week 8						
	S-1	S1-S7	B1	B2	B3	B4	B5	B6	D1 & D2						D-2	D1	D2	D3	D4	D5	PT1	PT2
Accelerometer applied		X																				
Accelerometer removed- MVPA			X																			
Consent Form	X																					
Fasting glucose screening	X																					
Lipids- Screening	X																					
VO2 max					X															X		
Bod Pod							X														X	
DXA							X														X	
OGTT							X														X	
Clamp								X														X
Insulin								X														X
Glucose								X														X
Myokines								X	X						X	X	X	X				X
RMR								X														X
1 RM				X									X		X							
Diet (55%Cho/15%Pro/30&Fat)			X	X	X	X	X										X	X	X	X	X	
Exercise training									X	X	X	X	X	X	X	X				X		

Subjects were instructed to report the Monday after the baseline hyperinsulinemic euglycemic clamp for the first day of training. Exercise training was composed of 3 combined exercise training sessions (aerobic & resistance) per week that lasted for approximately 75 minutes per session for a total of eight weeks. During the first week of training, blood was drawn during fasted conditions before and immediately after the first aerobic exercise bout (Table 3. day 1 of week 1) and first resistance exercise bout (Table 3. training day 2 of week 1) to assess myokine secretion after one acute bout of aerobic and resistance training. Similarly, blood was also drawn before and immediately after the last bout of aerobic (Table 3. day 1 of week 8) and resistance (Table 3. day 3 of week 8) exercise during the last week of exercise training to assess the effects of 8 weeks of combined exercise training on acute myokine response to exercise training. One repetition maximum was assessed at baseline (day 2), Mid-intervention (week 5, D1) and post-intervention (week7, D2 (Table 1). Subjects were provided with a standard diet, five days before the post intervention

clamp. Similar to baseline testing, insulin sensitivity, metabolic flexibility, body composition, complete metabolic panel, thyroid function, lipids, insulin, and myokine concentration were re-assessed during the post-intervention clamp protocol. A detailed description of these tests are provided below.

Table 4. Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. 18 ≤ Age ≤ 40 years 2. 18 ≤ BMI ≤ 30 kg/m^2 3. Both parents are Mexican/ Mexican-American 4. Sedentary lifestyle Less than 60 minutes/wk. of moderate to vigorous intensity physical activity (MVPA)	1. Evidence of significant cardiovascular disease or diabetes 2. A fasting blood glucose ≥ 100 mg/dl 3. Screening blood pressure ≥ 140/90 4. Hyperlipidemia- Total cholesterol ≥ 240mg/dl 5. Use of drugs affecting energy metabolism or body weight 6. Excess alcohol, drug abuse, and smoking 7. Eating disorder or eating attitudes interfering with study 8. Unwillingness to be abide by randomization

Table 5. Screening measurements

Measurement	Method
Sedentary physical activity level	Physical activity questionnaire & time spent in moderate to vigorous physical activity (MVPA) <60 minutes per week.
Fasting Blood Glucose	Blood sample via lancet stick/analysis via true result blood glucose meter
Lipid Profile (screening) (HDL, LDL, Total Cholesterol)	Blood sample via lancet stick/analysis through point of care testing (Alere, Cholestech LDX)
Blood Pressure	Automated blood pressure device
Body Mass Index (BMI)	Height & weight measurements
Medical History	Questionnaire

Table 6. Study variables

Variable	Method of Measuring
Body Composition	Air displacement plethysmography (BodPod) & dual energy X-ray absorptiometry (DXA)
Maximal Aerobic Capacity	Standard graded exercise
Insulin Sensitivity	Hyperinsulinemic-euglycemic clamp
Glucose tolerance	Oral glucose tolerance test (OGTT)
Metabolic Flexibility	Indirect calorimetry- change in respiratory quotient (delta RQ) from fasting to insulin stimulated condition
Resting Metabolic Rate	Indirect calorimetry
Plasma Lipids (HDL, LDL, Cholesterol, Triglycerides)	Laboratory Corporation of America ©
Myokine & Cytokine Concentration	MYOMAG-56K | MILLIPLEX MAP Human Myokine Magnetic Bead Panel
Fasting Insulin and Glucose Concentration	Laboratory Corporation of America ©

Anthropometric Measurements

Height (cm) and weight (kg) measurements were taken to determine body mass index (BMI, kg/m^2) before and after the 8 weeks of combined exercise training. Waist-to-hip ratio (WHR, Waist-cm/Hip-cm) was calculated by measuring the narrowest part of the waist, right above the navel and dividing this value by the circumference of the hips or at the greater trochanter (Appendix G).

Physical Activity Measurement

Sedentariness of the participants was confirmed via questionnaire (Appendix H) as well as sedentary level of physical activity was determined by calculating the time spent in moderate to vigorous physical activity (<60 minutes per week) [82] (Appendix I). ActiGraph activity Monitor (GT3XP-BTLE 2GB) was clipped to the belt or pants of the subjects closest to the anterior superior iliac crest and was worn for 7 days (Monday-

Sunday) including sleep time. After the 7-day wear time (>90% wear time), the subject reported to the research facility and participant's physical activity was quantified.

Dietary Control

Breakfast, lunch, dinner, and snacks were measured, weighed and prepared by day and separated by meal into their daily containers (Appendix J). Subjects were maintained on the diet for the five days prior to the baseline and five days before the end of the intervention to minimize the effects of diet on insulin sensitivity and plasma markers. Meals were designed to comply with the USDA 2010 Dietary Guidelines for Americans and individualized to participant preferences. This consisted of ~55% energy from carbohydrate, ~15% energy from protein and ~30% energy from fat (with no more than 10% from saturated fat). The Mifflin St Jour equation was utilized to match the participants estimated energy requirements with the diet provided. During the exercise training, participants were encouraged to follow the USDA 2010 Dietary Guidelines for Americans (as detailed above) and to consume an energy balanced diet.

Air Displacement Plethysmography (BodPod):

Participants were asked to sit in an air displacement plethysmography chamber (BodPod) (Life Measurement, INC. Concord, CA) for about 45 seconds, maintain the sitting position, and breathing as normally as possible. Compression/tight fitting clothing such as tights and spandex, along with a swimming cap were required. The subject's body mass, body volume, or amount of air displaced were determined to calculate the percentage of fat and fat free mass.

Dual Energy X-ray absorptiometry (DXA)

Subjects were asked to lie supine on the scanner table of a GE Dual Energy X-ray Absorptiometry (GE Medical Systems. Madison, WI) system. Arms were kept close to the body while knees and ankles were lightly strapped to prevent movement in the lower extremities [83]. The scanner bar traveled from head to toe. The time spent for the measurement was about 15 to 20 minutes, depending on the body the size of the subjects. Lean mass, fat mass, bone mineral density (BMD), and bone mineral content (BMC) measurements were obtained.

Maximal Aerobic Capacity

Maximal aerobic capacity (VO_{2max}) was measured using a standardized graded treadmill laboratory protocol. Subjects began the test on a treadmill at 3 mph and a 3% incline for the first 3 minutes to determine the oxygen consumption at an absolute workload, it was followed by a 2-minutes warm up at 5 mph at 0% incline. The remainder of the test was performed at a comfortable speed (5-6 mph) chosen by the participant while increasing 1% incline every minute. Subjects' rate of perceived exertion (RPE) and heart rate (HR) were monitored throughout the test. Once the subject reached volitional exhaustion the test was terminated. Standard measurements of VO_2 and VCO_2 were used to determine respiratory exchange ratio (RER) throughout the exercise test using a Parvomedics TrueOne 2400 metabolic measurement cart (Salt Lake City, UT). Maximal aerobic capacity was determined once the subject has met 2 out of the 4 following criteria: 1) respiratory exchange ratio (RER) >1.1, 2) $\pm$10 beats per minute from age predicted maximal heart rate, 3) RPE >17 as demonstrated by

Evardesen et al., 2014, 4) plateau in oxygen consumption with increased intensity for 1 minute [84]. (Appendix K).

One Repetition Maximum

One repetition maximum strength (1-RM) was performed before the first week and on the last week of the exercise training period. Upper body strength was assessed though a 1-RM bench press and lower body strength was assessed through a 1-RM back leg strength dynamometer. Mid-term 1-RM testing was administered on the first day of training of the fifth week.

Hyperinsulinemic-euglycemic Clamp

The hyperinsulinemic euglycemic clamp is considered the gold-standard measurement for insulin sensitivity [85]. Participants were asked to arrive at the UTEP Health Sciences building following an overnight (12-h) fast. A catheter was inserted into a forearm vein for infusion of insulin and glucose; another catheter was inserted into a contralateral dorsal hand vein warmed in a heating blanket for arterialized-venous blood sampling. Prior to insulin and glucose infusion, fasting insulin and blood glucose samples (6 ml for each) were obtained. A primed continuous infusion of regular insulin (2.5 ml) (Humulin, Eli Lilly and Co., Indianapolis, IN) was added to a 250 ml saline bag and was administered at an initial rate of 313 mU/min/m^2. This large bolus of insulin was used in order to suppress β-cell insulin secretion. The initial insulin loading dose of 80 mU/min/m^2 was calculated by multiplying the body surface area (BSA) by the desired insulin dose (80 mU/min) then dividing this product by 1000 to account for the milliliters

and multiplying the remainder by 60 (minutes in an hour), this yields the insulin infusion rate (mL/h). Insulin was infused along with a 20% dextrose solution to maintain blood glucose at a concentration of 90 mg/dl throughout the clamp period. A 0.5 mL blood sample from the forearm vein was drawn every 5 minutes throughout the duration of the clamp. A waste sample of 1.5 times the dead space of the micro-bore extension set (approximately 1 mL) was pulled prior to each collection of the 0.5 mL blood sample. The samples were analyzed immediately for glucose concentrations (YSI 2300 STAT Plus Glucose/Lactate Analyzer). Insulin concentration were measured from blood drawn pre- and post-clamp. Insulin sensitivity was determined from the glucose disposal rate (mg/kg estimated metabolic size (EMBS)/min) on the last 15 minutes of the clamp [86]. Following cessation of insulin administration, the final glucose infusion rate (ml/hr) was increased by 30% for 10 mins to prevent hypoglycemia. If euglycemia was maintained, the glucose infusion rate was decreased to 10% of the final glucose infusion rate for 10 minutes. At the end of this 15-minute period, if euglycemia was maintained (i.e. 3 consecutive concentrations within 10mg/dl), there was cessation of glucose infusion. The participant continued to be monitored for 30 minutes. Blood samples were collected at 10-minute intervals. Following the 2-hour procedure, the participant was given a snack and beverage and allowed to leave the laboratory after consuming the meal.

Resting Metabolic Rate

Resting metabolic rate (RMR) was measured via indirect calorimetry using a Parvomedics TrueOne 2400 metabolic measurement cart (Salt Lake City, UT). On the same day as the clamp, participants' RMR and respiratory quotient (RQ) were

determined by indirect calorimetry. Participants were placed into a semi-recumbent position and a hood was placed over their head for measurement of oxygen utilized and carbon dioxide produced. Participants were instructed to breathe normally during this 30-min collection period. This procedure was completed in fasting conditions and again during the last 30-min of the clamp (insulin stimulated conditions) for the determination of metabolic flexibility.

Metabolic Flexibility

The respiratory quotient (RQ) values were acquired through indirect calorimetry using the hood and canopy method in order to determine the volume of CO_2 expired and volume of O_2 inspired to calculate metabolic flexibility, as described before [86]. Delta RQ was derived by subtracting the fasting RQ from the insulin stimulated RQ during the clamp. This determined to what degree subjects were able to shift from fat to carbohydrate oxidation during an insulin stimulated condition.

Oral Glucose Tolerance Test (OGTT)

Participants were asked to arrive at the UTEP Health Sciences building and to avoid eating, drinking, smoking or strenuous exercise for 10-12 hours prior to testing. Participants were asked to remain seated while a fasting blood sample was collected via finger stick. The participant then orally ingested 75 grams of glucose as quickly as possible. Blood samples were collected at timed intervals of 15, 30, 60, 90, 120, 150, and 180 minutes following ingestion of the glucose. Blood glucose was analyzed via true result handheld blood glucose meter. Glucose tolerance was assessed by

calculating the area under the curve determined from blood glucose concentrations during the 3 hours of the test (Appendix L). The area under the curve was calculated by using the trapezoidal rule in which the integral was defined, then divided into segments and deriving the sum of the segments.

Fasting glucose and Fasting insulin

On the same day of the clamp, an intravenous blood sample was obtained from the IV line for analysis of fasting insulin and fasting glucose. Fasting blood glucose was analyzed via the YSI 2300 STAT PLUS glucose and L-Lactate analyzer. Fasting blood insulin was analyzed by Laboratory Corporation of America (Burlington, NC.).

Lipid Profile

On the same day of the clamp, an intravenous blood sample was obtained from the IV line for analysis of low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides (TG) and total cholesterol. Blood samples were evaluated by Laboratory Corporation of America (Burlington, NC.).

Myokine and Cytokine Concentration

On the same days of the clamp, an intravenous blood sample was obtained from the IV line for analysis of myokine concentrations at baseline and at the end of the exercise intervention. Additionally, intravenous blood samples were obtained before and immediately after a bout of aerobic and resistance exercise at the beginning and at the end of the 8-week exercise training intervention (Table 3) to evaluate the effects of 8 weeks of combined exercise training on acute exercise response of myokines. Blood samples were collected and centrifuged to isolate serum and were stored at -80 °C. Serum for each time point were pooled for myokine analyses for FH- and FH+ groups. Serum IL-15, IL-6 and, Myostatin concentrations were measured using a magnetic bead-based multiplex assay (milliplex® MAP Human Myokine Magnetic Bead Panel., R&D systems, Minneapolis, MN, USA).

Exercise Intervention

All participants exercised at the UTEP Research Fitness Facility located within the Ross Moore building. All exercise sessions were supervised by trained graduate students to ensure safety and compliance to exercise prescriptions. Exercise training consisted of 8 weeks of combined aerobic and resistance training performed 3 days of the week (30 min aerobic and 30 min resistance per training day). For the aerobic training, subjects began training at 55% of their maximum aerobic capacity (VO_2max), increasing 5% every two weeks up to 70% of VO_2max. For the resistance training, subjects performed 3 upper-body and 3 lower-body resistance exercise with intensity set at 3 sets of 8 repetitions. Exercises were rotated from a pool of 20 exercises (Lower

body exercises: barbell squat, dumbbell squat, dumbbell goblet squats, dumbbell sumo squats, dumbbell lunges, barbell deadlift, dumbbell deadlift, weighted glute bridges; Upper body exercises: flat barbell bench press, incline barbell bench press, flat dumbbell bench press, incline dumbbell bench press, Latissimus pull down, cable row, dumbbell row, barbell row, dumbbell shoulder press, dumbbell lateral raises, dumbbell front raises, triceps extensions). Measurements of strength were performed before the first week (baseline), on the first day of training of the fifth week (mid-intervention), and on the last week (post-intervention) of the exercise training period (1RM bench press & back leg strength dynamometer) (Appendix E).

Statistical Analysis

Statistical analyses were performed using GraphPad Prism, version 6.0 (GraphPad Software Inc, La Jolla, California). Two-way ANOVA with repeated measures was used to compare groups (FH-, FH+), time (before vs. after intervention) and group by time effects. Results are reported as mean ± SEM, significant differences were to be assumed for $p<0.05$.

Chapter 3: Results

Table 7. Summarizes the outcome measures of study participants (FH- (n=9) and FH+ (n=10)) who completed the 8-week combined exercise training intervention. Compliance rate was set at 100%. Three participants were excluded from the analyses due to non-compliance to the exercise training sessions. Age (FH- 21.89 ± 0.60 yrs, FH+ 23.41 ± 0.86 yrs; p=0.25), BMI (FH- 27.51 ± 1.68 Kg/m^2, FH+ 26.64 ± 1.02 Kg/m^2; p=0.65), fat free mass (FH- 54.82 ± 2.28 kg FH+ 51.14 ± 1.58 kg; p=0.19), and fat mass (FH- 23.44 ± 3.03 kg, FH+ 24.23 ± 1.97 kg; p=0.82) were not significantly different between groups at baseline. Insulin sensitivity between groups was not significantly different at baseline (FH- 2.99 ± 0.27; FH+ 3.63 ± 0.50 ml/kg estimated metabolic body size (EMBS), p=0.3). Metabolic flexibility between groups was not significantly different at basline (FH- 0.07 ± 0.01; FH+ 0.08 ± 0.01, p=0.72). Insulin sensitivity significantly improved in both groups (FH- 2.99 ± 0.27 to 3.89 ± 0.28 ml/kg (EMBS), p=0.02; FH+ 3.63 ± 0.50 to 4.82 ± 0.51 ml/kg EMBS; p=0.002). Improvement in insulin sensitivity expressed as percent (%) change were not significantly different between groups (FH- 34.90 ± 11.00 % vs. FH+ 40.66 ± 12.19 %; p>0.05). Metabolic flexibility did not improve in either FH- or FH+ groups (FH- 0.07 ± 0.01to 0.09 ± 0.01, p=0.71; FH+ 0.08 ± 0.01 to 0.11 ± 0.02, p=0.24). Regardless of normal glucose tolerance (blood glucose <140 mg/dl, 2 hours post glucose ingestion during OGTT), the FH+ group displayed a significantly higher blood glucose area under the curve 2 hours post glucose load after the baseline OGTT test (FH- 217.91 ± 5.39 AUC vs. FH+ 264.38 ± 12.67 AUC, p=0.004) as well as 3-h after glucose ingestion (FH- 307.09 ± 6.14 vs FH+ 354.12 ± 13.5, p=0.007). The FH+ group significantly decreased glucose AUC during the 2h-OGTT (264.38 ± 12.67 to 237.54 ±

11.77 AUC, p=0.002) after 8-weeks of combined exercise training. Fasting insulin significantly decreased (12.9 ± 2.45 to 10.12 ± 1.59 mIU/L, p=0.02) in the FH- group. HOMA-IR was not significantly different at baline between groups (FH- 2.51 ± 0.51 % vs. FH+ 1.92 ± 0.19 %; p>0.97). HOMA-IR significantly improved in the FH- group (2.51 ±0.51 to 1.97 ± 0.32 AU, p=0.03). Improvement in body weight expressed as percent change was significantly different between groups with the FH- group having a significant higher increase (FH- 3.42 ± 0.80 % vs. FH+ 0.95 ± 0.68 %; p=0.03). Percent body fat significantly decreased in the FH+ group (FH+ 31.63 ± 2.06 to 30.01 ± 1.9 kg, p=0.005). Fat free mass significantly increased in both groups (FH- 54.82 ± 2.28 to 56.52 ± 1.87 kg, p=0.02, FH+ 51.14 ± 1.58 to 53.42 ± 1.8 kg, p=0.001. Aerobic fitness significantly increased in the FH+ group (3.57 ± 0.16 to 3.82 ± 0.16 L/min p=0.001; 44.48 ± 1.82 to 47.18 ± 2.00 ml/kg/min p=0.01)) while the FH- group did not increase aerobic fitness (3.84 ± 0.23 to 3.97 ± 0.21 L/min p=0.11; 46.25 ± 1.55 to 47.51 ± 0.98 ml/kg/min p=0.33) Upper body strength (FH- 155.00 ± 20.83 to 181.10±21.13 lb, p=0.0001; FH+ 148.50 ± 16.87 to 178.00 ± 16.75 lb, p=0.0001) and lower body strength (FH- 354.44 ± 31.97 to 416.67 ± 27.55 lb, p=0.0006; FH+ 356.00 ± 20.18 to 419.50 ± 15.99 lb, p=0.0003) significantly increased in both groups. High density lipoproteins (HDL) significantly increased (31.44 ± 2.21 to 35.00 ± 2.36 mg/dl, p=0.03) in the FH- group. Total cholesterol to HDL ratio significantly improved (4.57 ± 0.61 to 4.06 ± 0.60 in mg/dl, p=0.03) the FH+ group. Low density lipoprotein to high density lipoprotein ratio also significantly improved (2.77 ± 0.48 to 2.42 ± 0.46 mg/dl, p=0.03) in the FH+ group

Table 7.

	FH-		Basline vs 8-weeks	FH+		Basline vs 8-weeks	FH- vs FH+	Group Effect	Time Effect	Interaction Effect
	Baseline	8-weeks	p-value	Baseline	8-Weeks	p-value	Pre-intervention	p-value	p-value	p-value
Number of Subjects	9	9		10	10		0.25			
Age	22.5±0.81			23.9±0.85			0.35			
Height (cm)	173.82 ± 1.46			174.24 ± 1.46						
Body weight (Kg)	79.34 ± 4.88	81.95 ± 4.88	0.0008***	79.00 ± 2.81	79.66 ± 2.57	0.44	0.95	0.81	0.0009***	0.02*
BMI (kg/m2)	27.51 ± 1.68	27.81 ± 1.64	0.38	26.63 ± 1.02	26.70 ± 1.01	0.94	0.65	0.6	0.26	0.47
Body fat (%)	29.04 ± 2.33	27.97 ± 2.28	0.08	31.63 ± 2.06	30.01 ± 1.9	0.005**	0.41	0.45	0.001***	0.43
Body fat (kg)	23.44 ± 3.03	23.51 ± 3.08	0.98	24.23 ± 1.97	23.21 ± 1.82	0.1	0.82	0.94	0.19	0.14
Lean mass (kg)	54.82 ± 2.28	56.52 kg ± 1.87	0.02*	51.14 ± 1.58	53.42 ± 1.8	0.001**	0.19	0.21	0.0001****	0.48
Waist to Hip Ratio (WHR)	0.87 ± 0.01	0.85 ± 0.01	0.18	0.86 ± 0.01	0.84 ± 0.01	0.26	0.56	0.62	0.03*	0.83
BMC (g)	3069.44 ± 133.72	3092.3 ± 151.1	0.87	2945.67 ± 127.60	3034.0 ± 120.1	0.13	0.5	0.62	0.11	0.33
BMD (g/kg2)	1.23 ± 0.03	1.24 ± 0.03	0.89	1.23 ± 0.04	1.23 ± 0.04	0.46	0.86	0.89	0.28	0.64
Tryglycerides (mg/dl)	152.3 ± 21.87	161.1 ± 20.42	0.71	133.0 ± 21.05	113.30 ± 20.4	0.18	0.53	0.25	0.5	0.09
Cholesterol (mg/dl)	142.8 ± 6.83	151.3 ± 8.89	0.27	159.8 ± 12.85	152.60 ± 11.61	0.35	0.27	0.53	0.86	0.059
High-density Lipoproteins (HDL)	31.44 ± 2.21	35.00 ± 2.36	0.03*	38.3 ± 3.47	41.1 ± 3.47	0.09	0.12	0.13	0.00***	0.69
Low-density lipoproteins (LDL)	79.56 ± 6.11	82.33 ± 5.68	0.8	95.0 ± 11.41	88.70 ± 9.51	0.31	0.26	0.37	0.59	0.17
Total Cholesterol/HDL	4.71 ± 0.35	4.42 ± 0.27	0.3	4.56 ± 0.61	4.05 ± 0.60	0.03*	0.84	0.71	0.01**	0.44
LDL/HDL Ratio	2.62 ± 0.24	2.42 ± 0.19	0.31	2.76 ± 0.48	2.41 ± 0.46	0.03*	0.8	0.89	0.01**	0.46
Fasting glucose (mg/dl)	77.29 ± 1.95	78.10 ± 1.43	0.81	80.48 ± 1.70	80.33 ± 1.50	0.99	0.23	0.22	0.73	0.62
Fasting glucose (mmol/l)	4.29 ± 0.10	4.34 ± 0.07	0.81	4.47 ± 0.09	4.46 ± 0.08	0.99	0.23	0.22	0.73	0.62
Fasting Insulin (mIU/L)	12.9 ± 2.45	10.12 ± 1.59	0.02*	9.62 ± .87	9.53 ±1.09	0.99	0.2	0.37	0.052	0.06
2h-OGTT (AUC)	247.4 ± 11.90	227.5 ± 6.60	0.29	302.4 ± 11.01	237.5 ± 11.77	0.002**	0.0002***	0.01**	0.0003***	0.02*
3h-OGTT (AUC)	307.1 ± 6.14	302.1 ± 16.25	0.93	354.1 ± 13.5	323.9 ± 14.61	0.09	0.007**	0.23	0.1	0.04*
HOMA-IR (AU)	2.51 ± .51	1.97 ± 0.32	0.03*	1.92 ± 0.19	1.88 ± 0.21	0.97	0.28	0.45	0.055	0.09
HOMA-β (AU)	358.7 ± 67.73	246.4 ± 33.8	0.02*	213.3 ± 24.93	217.3 ± 32.97	0.99	0.051	0.1	0.07	0.058
QUICKI (AU)	0.34 ± 0.01	0.35 ± 0.00	0.69	0.35 ± 0.00	0.35 ± 0.00	0.86	0.84	0.88	0.37	0.82
Insulin sensitivity ((mg/kg EMBS/min)	2.995 ± .27	3.88 ± 0.28	0.02*	3.63 ± .50	4.82 ± 0.51	0.002**	0.3	0.17	0.0002***	0.5
Metabolic Flexibility (△RQ)	0.07 ± 0.01	0.09± 0.01	0.71	0.08 ± 0.01	0.11 ± 0.02	0.24	0.72	0.38	0.12	0.59
Resting Metabolic Rate (Kcal)	2077 ± 119.5	2074 ± 61.05	0.99	1966 ± 50.62	2061 ± 87.36	0.33	0.29	0.4	0.27	0.4
Resting Metabolic Rate (Kcal/FFM)	37.6 ± 1.16	36.6 ± 1.00	0.6	38.6 ± 1.27	38.9 ± 1.52	0.95	0.57	0.32	0.65	0.4
Resting Metabolic Rate (Kcal/BW)	25.2 ± 0.81	25.0 ± 1.06	0.96	24.9 ± 0.72	25.4 ± 0.81	0.8	0.82	0.96	0.8	0.56
Upper-body strength (Lbs)	155.0 ± 20.83	181.1 ± 21.13	0.0001****	148.5. ± 16.87	178.00 ± 16.75	0.0001****	0.8	0.85	0.0001****	0.47
Lower-body strength (Lbs)	354.4 ± 31.98	416.7 ± 27.55	0.0006***	356.00 ± 20.18	419.50 ± 15.99	0.0003***	0.96	0.94	0.0001****	0.94
Aerobic Fitness (ml/kg/min)	46.25 ± 1.55	47.51 ± 0.98	0.33	44.48 ± 1.82	47.18 ± 2.00	0.01**	0.47	0.65	0.005**	0.26
Aerobic Fitness (L/min)	3.84 ± 0.23	3.97 ± 0.21	0.11	3.57 ± 0.16	3.82 ± 0.16	0.001***	0.25	0.44	0.0005***	0.18
Fasting Substrate Utilizarion (RQ)	0.72 ± 0.01	0.69 ± 0.02	0.28	0.71 ± 0.01	0.72 ± 0.01	0.88	0.068	0.81	0.44	0.18
Physical Activity Level (PAL)	0.38 ± 0.17			0.69 ± 0.44			0.48			

ANOVA p<0.05*, p<0.01**, p<0.001***, p<0.0001****, T-test Kcal/FFM- Kilocalories/Fat Free Mass; Kcal/FFM- Kilocalories/Body Weight.

Improvement in Insulin Sensitivity after 8-Weeks of Combined Exercise Training

Insulin sensitivity significantly improved in both groups (FH- 2.99 ± 0.27 to 3.89 ± 0.28 mg/kg EMBS/min, p=0.02; FH+ 3.63 ± 0.50 to 4.82 ± 0.51 mg/kgEMBS/min, p=0.002, Figure 2A) after 8-weeks of combined exercise training. Change in insulin sensitivity between FH- and FH+ did not differ when expressed as delta (Δ) (FH- 0.89 ± .25 ml/kg/EMBS; FH+ 1.19 ± 0.35 ml/kg/EMBS, p=0.50 (Figure 2B) or percent change (FH- 34.90 ± 11.00% vs. FH+ 40.66±12.19%; p>0.05, Figure 2C).

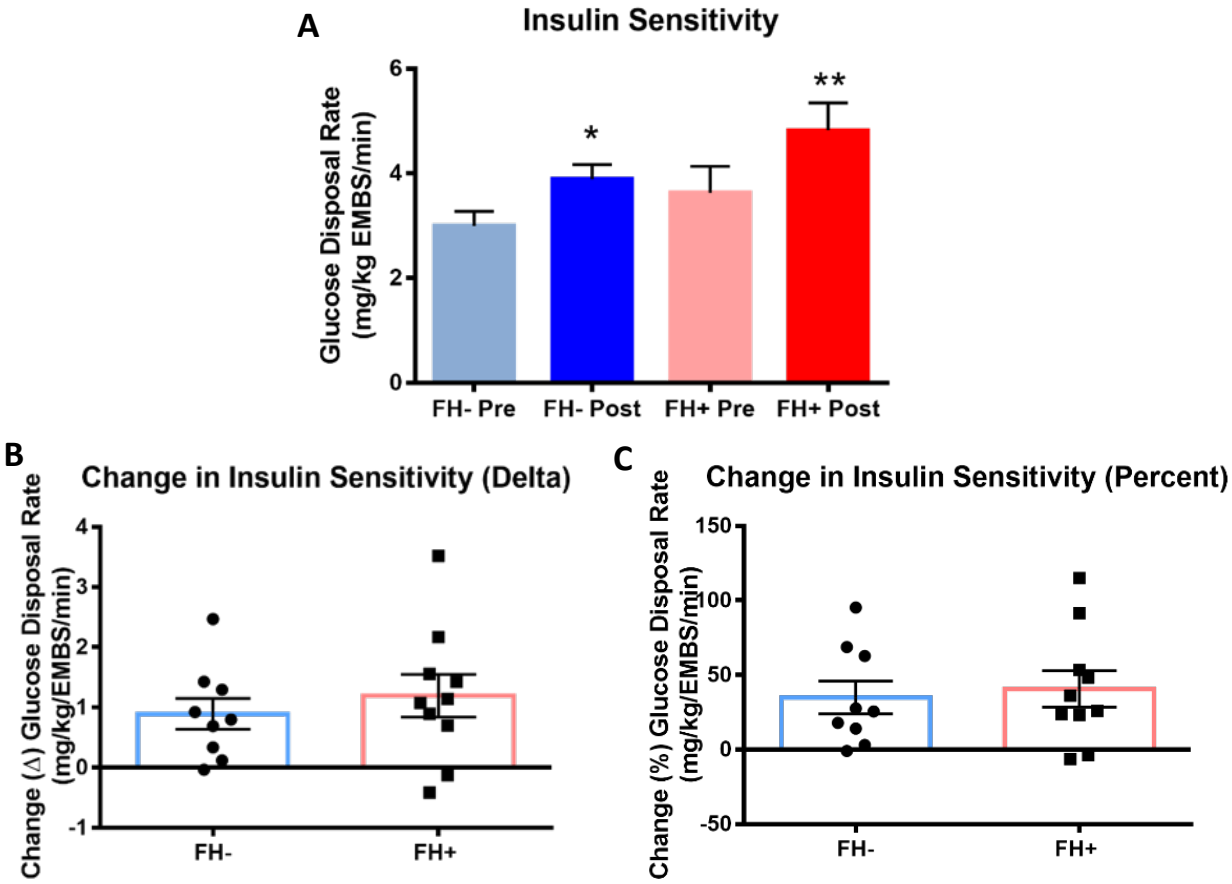

Figure 2 (A). Healthy normoglycemic individuals with (FH+) and without (FH-) a family history of type 2 diabetes significantly improved insulin sensitivity after 8-weeks of combined exercise training. (B). Individuals with (FH+) and without (FH-) a family history of type 2 diabetes did not differ in terms of change in insulin sensitivity. (C). Individuals with (FH+) and without (FH-) a family history of type 2 diabetes did not differ in improvement of insulin sensitivity.
EMBS: Estimated Metabolic Body Size, Data are means ± SEM. *p<0.05, **p<0.01

No change in Metabolic Flexibility after 8-Weeks of Combined Exercise Training

Metabolic flexibility, measured by change in respiratory quotient (ΔRQ) from fasting to insulin stimulated condition, did not change after 8-weeks of combined exercise training in participants without a family history of T2D (FH- 0.07 ± 0.01 to 0.09 ± 0.01, p=0.71; FH+ 0.08 ± 0.01 to 0.11 ± 0.06, p=0.24; Figure 3A). No change in metabolic flexibility was present in either group when expressed as delta (FH- 0.07 ± 0.01 to 0.09 ± 0.01, p=0.71; FH+ 0.08 ± 0.01 to 0.11 ± 0.02, p=0.24; Figure 3B). Metabolic flexibility did not change when expressed as percent change (FH- 9.97 ± 2.27 to 12.73 ± 2.69, p=0.47; FH+ 10.72 ± 1.93 to 15.81 ± 3.05, p=0.14; Figure 3C) Fasting substrate utilization did not change (FH- 0.72 ± 0.00 to 0.69 ± 0.01, p=0.07; FH+ 0.71 ± 0.01 to 0.71 ± 0.01, p=0.68; Figure 3D). Resting energy expenditure did not improve (FH- 2077.32 ± 119.5 to 2173.00 ± 61.05, p=0.99; FH+ 1965.0 ± 50.62 to 2061.40 ± 87.36, p=0.33; Figure 3E).

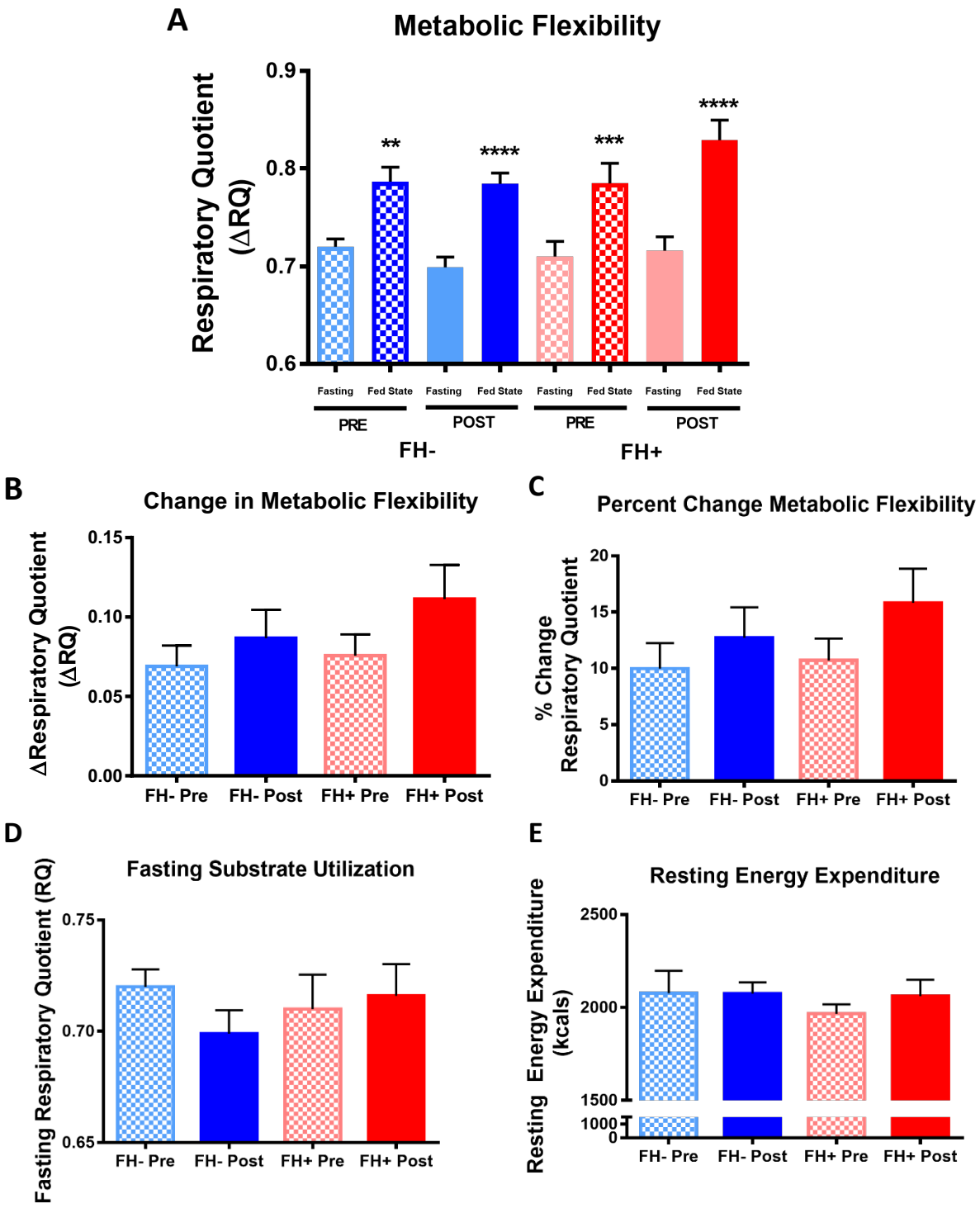

Figure 3(A). Healthy normoglycemic individuals with (FH+) and without (FH-) a family history of type 2 diabetes significantly ncreased respiratory quotient from fasting conditions to insulin stimulated conditions during pre and post intervention clamps. (B). Metabolic flexibility did not change in either group after 8 weeks of combined exercise. (C). Metabolic flexibility percent change remained unchanged for both groups. (D). Fasting substrate utilization did not change in either group. (E). Resting energy expenditure did not chage in either group. **p<0.001,*p<0.0001. ****p<0.001. Data are means ± SEM.**

Improvement in Performance after 8-Weeks of Combined Exercise

Upper body strength, measured by flat barbell bench press significantly increased for both groups (FH- 155.00 ± 20.83 to 181.10 ± 21.13 lb, p=0.0001; FH+ 148.50 ± 16.87 to 178.00 ± 16.75lb, p=0.0001; Figure 4A) after eight weeks of combined aerobic and resistance exercise training. Increase in upper body strength between FH- and FH+ groups were not different after 8-weeks of combined exercise training when expressed as delta (FH- 26.11 ± 2.97 lb vs. FH+ 29.50 ± 3.45 lb; p=0.47; Figure 4C) or percent change (FH- 19.28 ± 3.45 % vs. FH+ 22.59 ± 3.73 %; p=0.52, Figure 4E).

Lower-body strength, measured by Lower-body dynamometer increased significantly for both groups (FH- 354.44 ± 31.97 to 416.67 ± 27.55 lb, p=0.0006; FH+ 356.00 ± 20.17 to 419.50 ± 15.99 lb, p=0.0003; Figure 4B) after 8-weeks of combined exercise. Increase in lower body strength between FH- and FH+ groups were not different after 8-weeks of combined exercise training when expressed as delta (FH- 62.22 ± 17.71 lb vs. FH+ 63.50 ± 8.50 lb; p=0.94; Figure 4C) or percent change (FH- 21.95 ± 8.23 % vs. FH+ 19.36 ± 3.69 %; p=0.76, Figure 4F.

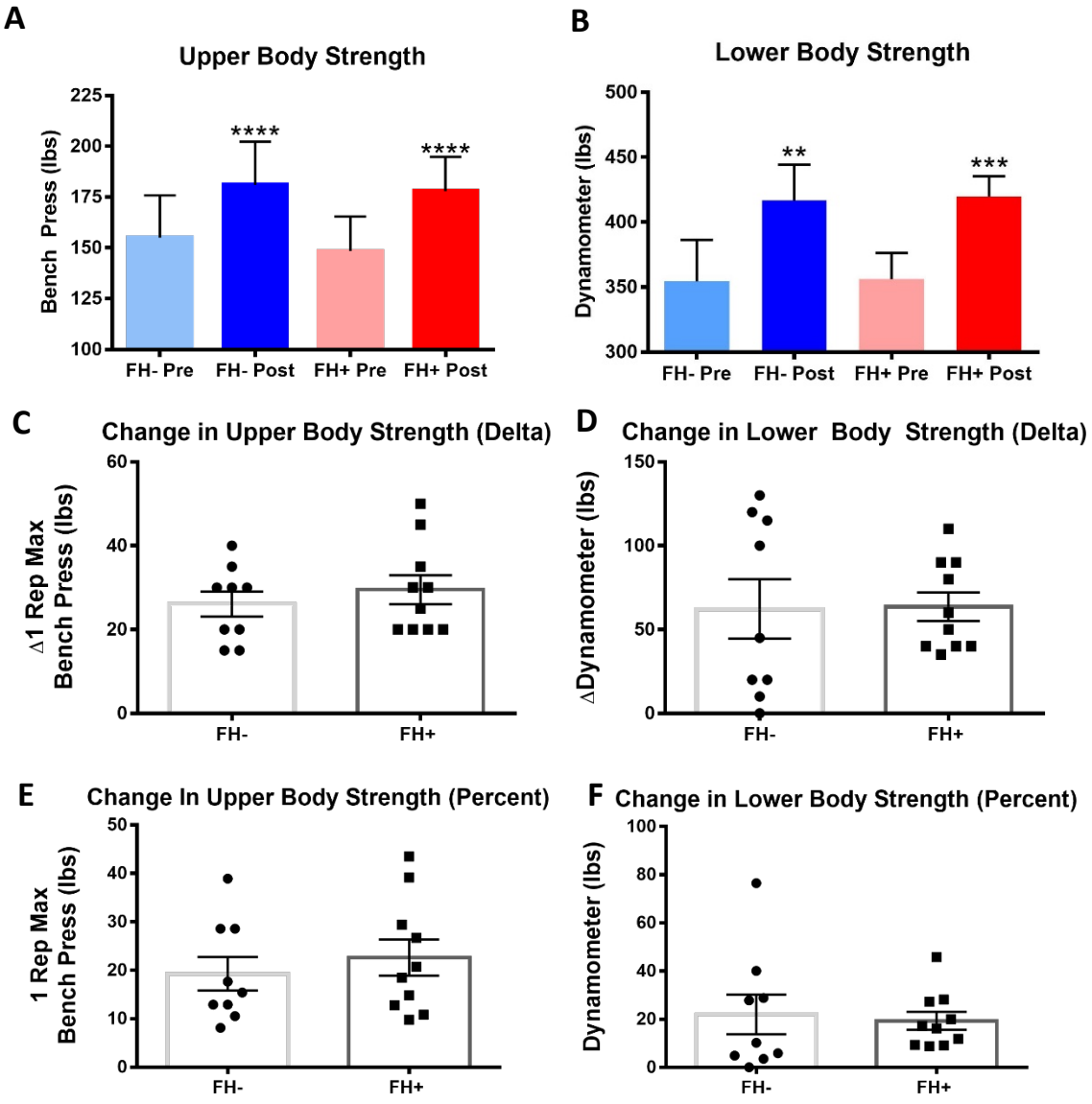

Figure 4 (A). Healthy normoglycemic individuals with (FH+) and without (FH-) a family history of type 2 diabetes significantly increased upper body strength after 8 weeks of combined exercise training. (B). Individuals with (FH+) and without (FH-) a family history of type 2 diabetes significantly increased lower body strength. (C). Subjects did not differ in terms of change (Δ) increase in upper body strength. (D). Subjects did not differ in terms of change (Δ) in crease in lower body strength delta. (E). Subjects did not differ in terms of percent change (%) in upper body strength. (F). Subjects did not differ in terms of percent change (%) in lower body strength. **p<0.001,*p<0.0001. ****p<0.00001, Data are means ± SEM.**

Improvement in Aerobic Fitness after 8-weeks of Combined Exercise Training

Aerobic fitness significantly increased in the FH+ group (3.57 ± 0.16 to 3.82 ± 0.16 L/min p=0.001; Figure 5A; 44.48 ± 1.82 to 47.18 ± 2.00 ml/kg/min p=0.01; Figure 6A) while the FH- group did not improve aerobic fitness (3.84 ± 0.23 to 3.97 ± 0.21 L/min p=0.11; Figure 5A; 46.25 ± 1.55 to 47.51 ± 0.98 ml/kg/min p=0.33; Figure 6A) after 8 weeks of combined exercise training. Increase in aerobic fitness between FH- and FH+ groups were not different after 8-weeks of combined exercise training when expressed as delta (FH- 0.13 ± 0.07 L/min vs. FH+ 0.25 ± 0.05 L/min; p=0.18; Figure 5B; 1.26 ± 0.98 ml/kg/min vs. 2.70 ± 0.79 ml/kg/min, p=0.46 Figure 6B) or percent change (FH- 3.98 ± 2.03 % vs. FH+ 7.39 ± 1.54 % L/min; p=0.19; Figure 5C; FH- 3.27 ± 2.43% vs. FH+ 6.19 ± 1.83 % ml/kg/min; p=0.34, Figure 6C).

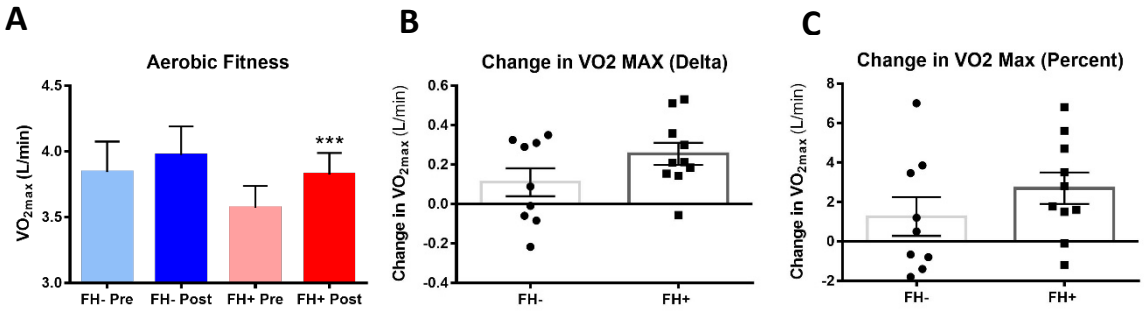

Figure 5. (A). Healthy normoglycemic individuals with (FH+) a family history of type 2 diabetes significantly increased aerobic fitness after 8-weeks of combined exercise training. (B). Healthy normoglycemic individuals with (FH+) and without (FH-) a family history of type 2 diabetes did not differ in terms of change (Δ) improvement in aerobic fitness. (C). Individuals with (FH+) and without (FH-) a family history of type 2 diabetes did not differ in terms of percent change (%) improvement in aerobic fitness. ***p<0.001, Data are means ± SEM.

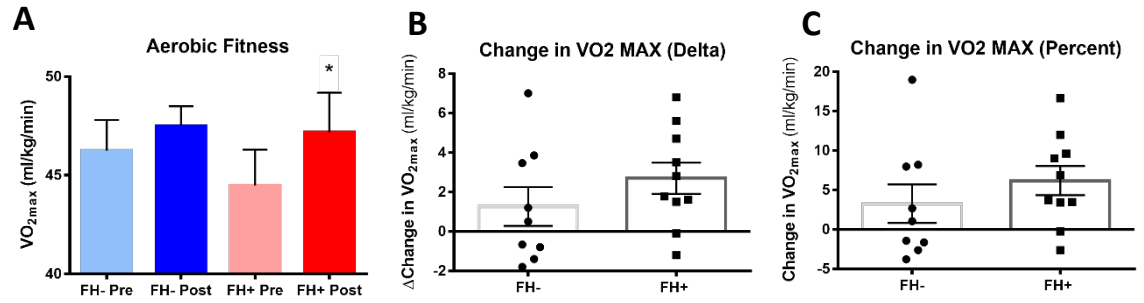

Figure 6 (A). Healthy normoglycemic individuals with (FH+) a family history of type 2 diabetes significantly improved aerobic fitness after 8-weeks of combined exercise training. (B). Individuals with (FH+) and without (FH-) a family history of type 2 diabetes did not differ in terms of change (Δ) in aerobic fitness. (C). Individuals with (FH+) and without (FH-) a family history of type 2 diabetes did not differ in terms of percent change (%) in aerobic fitness. *p<0.05, Data are means ± SEM.

Improvement in Body Composition after Eight Weeks of Combined Exercise

Body weight significantly increased in the FH- group (FH- 79.34 ± 4.88 to 81.95 ± 4.88 kg, p=0.0008; Figure 7A). Increase in body weight between FH- and FH+ groups after 8-weeks of combined exercise training when expressed as delta was significantly higher in the FH- group compared to the FH+ group (FH- 2.61 ± 0.64 kg vs. FH+ 0.66 ± 0.50 kg; p=0.02; Figure 8A). Increase in body weight expressed as percent change had a significnalty higher increase in the FH- group (FH- 3.42 ± 0.80 % vs. FH+ 0.95 ± 0.68 %; p=0.03; Figure 9A). Percent body fat significantly decreased in the FH+ group (FH+ 31.63 ± 2.06 to 30.01 ± 1.9 %, p=0.005 Figure 7B) and displayed a trend to decrease in the FH- group (FH- 29.04 ± 2.33 to 27.97 ± 2.28 kg, p=0.08 Figure 7B) after 8-weeks of combined exercise training. Lean mass significantly increased after 8-weeks of combined exercise training (FH- 54.82 ± 2.28 to 56.52 ± 1.87 kg, p=0.02, FH+ 51.14 ± 1.58 to 53.42 ± 1.8 kg, p=0.001; Figure 7C). After 8-weeks of combined exercise training there were no changes in fat mass (FH- 23.44 ± 3.03 to 23.51 ± 3.08 kg, p=0.98, FH+ 24.23 ± 1.97 to 23.21 ± 1.82 kg, p=0.10; Figure 7D)

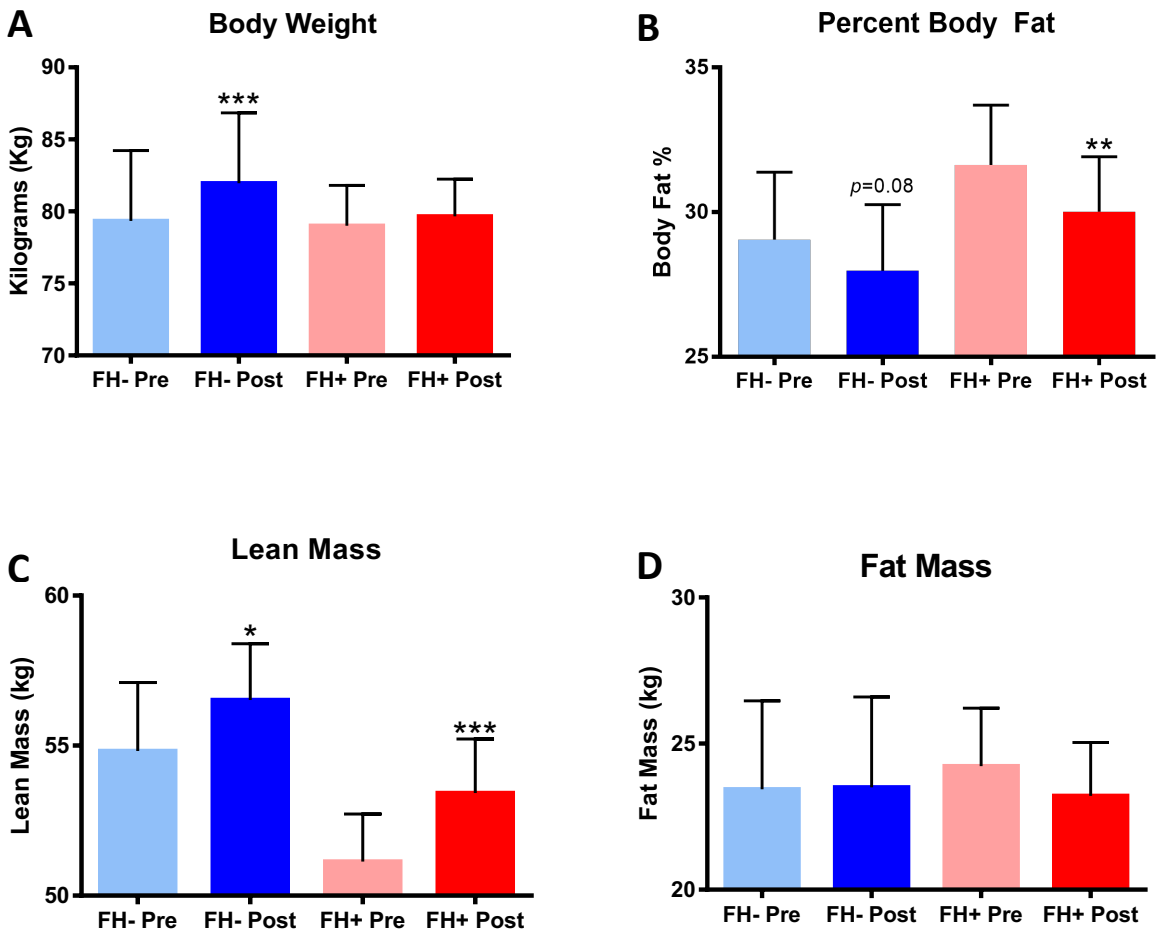

Figure 7. (A). Healthy normoglycemic individuals without (FH-) a family history of type 2 diabetes significantly increased total body weight after 8-weeks of combined exercise training. (B). Percent body fat significantly decreased in the FH+ group. (C).). Individuals with (FH+) and without (FH-) a family history of type 2 diabetes significantly increased Lean mass (D). No changes in fat mass was observed in either group. *p<0.05, **p<0.01, ***p<0.001. Data are means ± SEM.

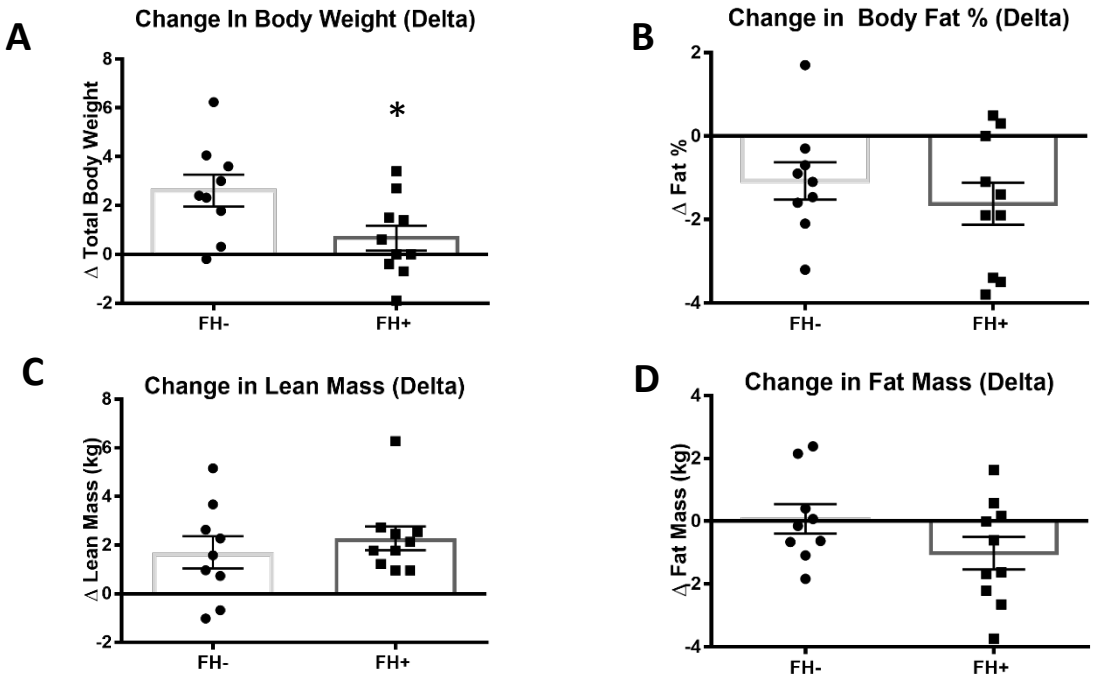

Figure 8 (A). Increase in body weight between FH- and FH+ groups when expressed as delta were not significantly different after 8-weeks of combined exercise training. (B). No difference in delta body fat % decrease between groups. (C). No difference in delta lean mass increase between groups was observed. (D). No difference in delta fat mass decrease between groups was observed after 8-weeks of combined exercise training. *p<0.05, Data are means ± SEM.

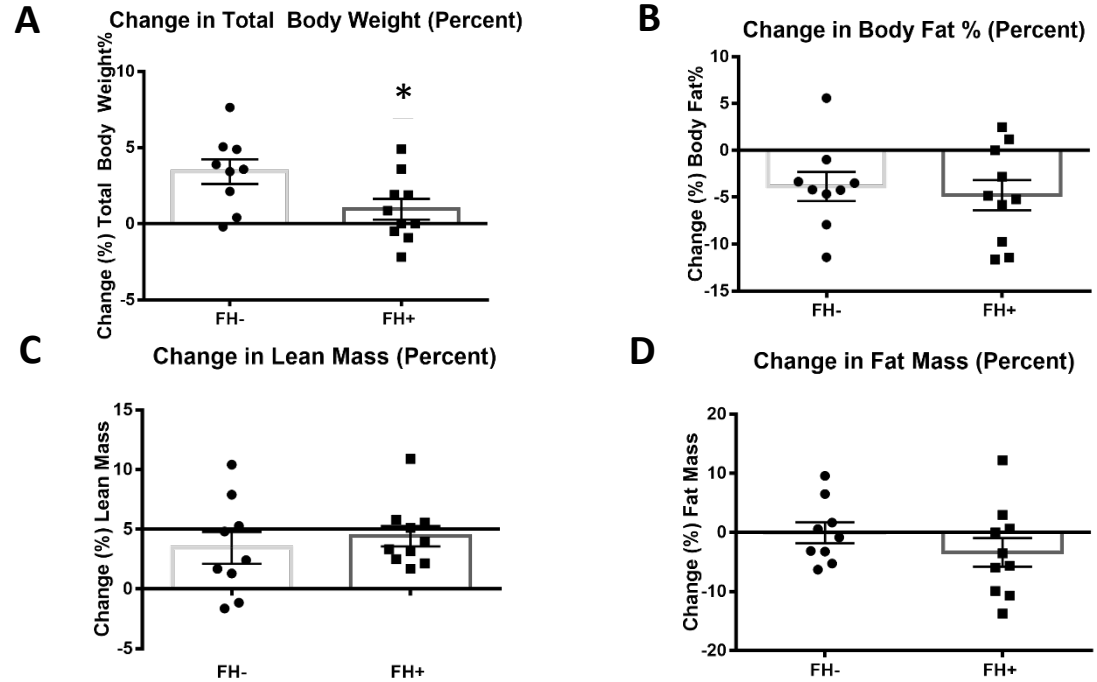

Figure 9. (A) Increase in body weight expressed as percent change were significantly different between groups with the FH- group having a significant increase after 8-weeks of combined exercise training. (B). No difference in percent change decrease in body fat % between groups. (C). No difference in percent change lean mass increase between groups. (D). No difference in percent change fat mass between groups. *p<0.05, Data are means ± SEM.

IL-6 Secretion after Exercise Training

Il-6 plasma concentrations from pooled samples that included all baseline time points for the FH- group appear to have been regulated (18.37 to 5.94 pg/ml) after 8 weeks of combined exercise training (chronic effect of exercise). FH+ individuals displayed virtually identical IL-6 plasma concentrations after 8-weeks of combined exercise training (11.58 to 11.49 pg/ml) compared to baseline. The effect of an acute bout of aerobic training at baseline, displayed minimal change in circulating IL-6 in the FH- group (7.5 to 6.85 pg/ml). An acute bout of resistance training at baseline displayed a potential regulation of circulating IL-6 (8.74 to 6.96 pg/ml) in the FH- group; as well as in the FH+ group (7.03 to 10.05 pg/ml) after 8-weeks of combined exercise training. Lastly, plasma IL-6 concentrations in the FH- group after an acute bout of resistance training following 8-weeks combined exercise appears to be unaltered (6.91 to 7.01 pg/ml); while the FH+ group displayed a regulatory effect after exercise (11.95 to 16.02 pg/ml).

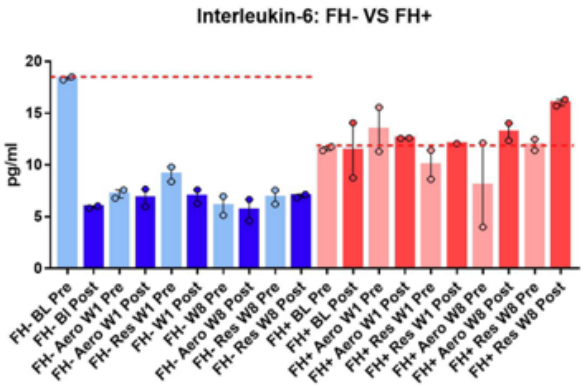

Figure 10. Chronic and acute effects of 8 weeks of combined exercise training on IL-6 pooled plasma concentrations.

IL-15 Secretion after Exercise Training

Plasma concentrations of IL-15 were below the detectable range in pooled samples in all conditions for the FH- group. Plasma IL-15 concentrations were only detectable at baseline for the FH+ group (3.65 pg/ml).

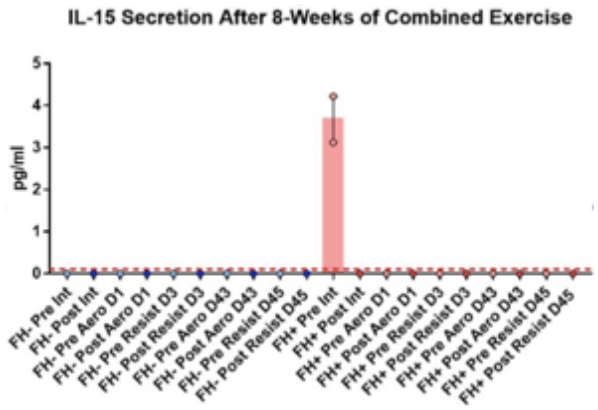

Figure 11. IL-15 pooled plasma concentrations were detectable only at baseline for the FH+ group.

IL-8 Secretion after Exercise Training

IL-8 plasma concentrations may have been regulated (19.84 to 7.06 pg/ml) in the FH- group after 8 weeks of combined exercise training (chronic effect of exercise). FH+ individuals displayed a potential upregulation in IL-8 plasma concentrations after 8-weeks of combined exercise training (11.24 to 12.66 pg/ml). The effect of an acute bout of aerobic training on IL-8 secretion before 8-weeks of combined exercise training may have not elicited a change on the FH- group, (7.75 to 7.98 pg/ml) as well as (13.47 to 12.49 pg/ml) in the FH+ group. An acute bout of resistance training before the 8-weeks of combined exercise training appeared to have regulated circulating IL-8 (11.02 to 8.88 pg/ml) in the FH- group; while the FH+ group's circulating IL-8 may have also been regulated by exercise (9.65 to 6.25 pg/ml) in IL-8 secretion after 8-weeks of combined

exercise training. Circulating IL-8 in the FH- group may have not been impacted after an acute bout of aerobic exercise after 8-weeks of combined exercise training (7.61 to 6.99 pg/ml). Circulating IL-8 in the FH+ group may have been regulated by an acute bout of aerobic exercise after 8-weeks of combined exercise training (8.26 to 12.25 pg/ml). Lastly, plasma IL-8 concentrations in the FH- group after an acute bout of resistance remained unchanged following 8-weeks combined exercise training (7.63 to 8.14 pg/ml); while it may have been regulated in the FH+ group (12.02 to 15.45 pg/ml).

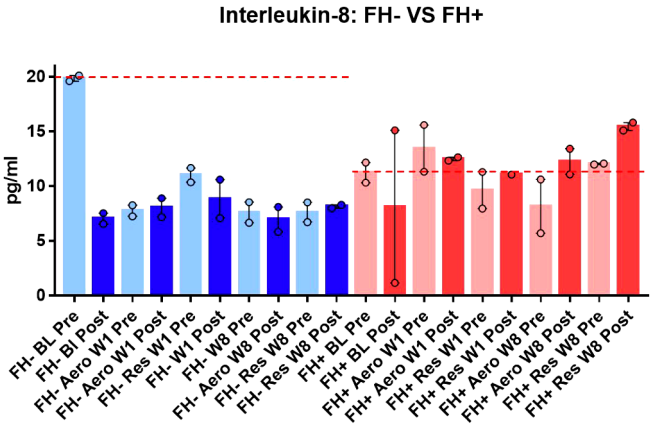

Figure 12. Chronic and acute effects of exercise training on IL-8 pooled plasma concentrations after 8-weeks of combined exercise.

Myostatin Secretion after Exercise Training

Myostatin pooled plasma concentrations were below the detectable range in samples at all time points for the FH- group. Myostatin concentrations appear to have been regulated after 8-weeks of combined exercise training (4553.0 to 494.02 pg/ml) in the FH+ group. Myostatin levels were also below baseline levels before an acute bout of aerobic exercise (473.53 pg/ml) before the 8-week exercise intervention, after an acute bout of resistance training (469.62 pg/ml), and before an acute bout of resistance training (500.17 pg/ml) after the 8-week exercise intervention.

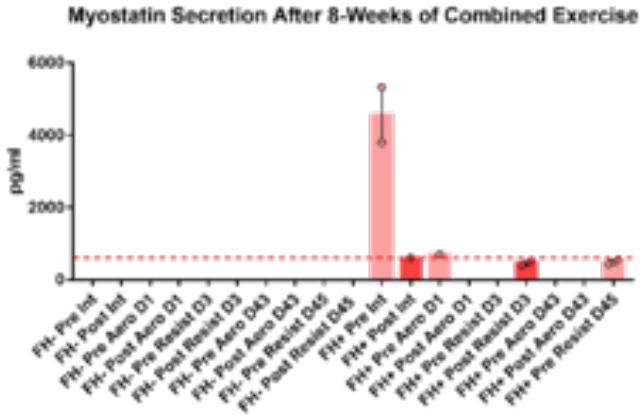

Figure 13. Myostatin pooled plasma samples after 8-weeks of combined exercise training.

Oncostatin M Secretion after Exercise Training

The effect of an acute bout of aerobic training on Oncostatin M (OSM) secretion before 8-weeks of combined exercise training displayed no regulation induced by exercise in the FH- group, (11.58 to 12.01 pg/ml) and a potential regulation in the FH+ group (5.96 to 11.2 pg/ml). An acute bout of resistance training before the 8-weeks of combined exercise training may have also regulated circulating OSM (17.24 to 8.69 pg/ml) in the FH- group as well as in the FH+ group (11.69 to 9.54 pg/ml) after 8-weeks of combined exercise training. Although sample replicate variability was evident, circulating OSM appears to have not been impacted (6.41 to 5.11 pg/ml) in the FH- group after an acute bout of aerobic exercise. The FH+ group also may have experienced a regulatory effect in circulating OSM concentrations after an acute bout of aerobic exercise following 8-weeks of combined exercise training (17.13 to 9.43 pg/ml). Lastly, plasma OSM concentrations in the FH- group appear to have been regulated (5.81 to 8.85 pg/ml) after an acute bout of resistance training following 8-weeks combined exercise. A change in OSM after 8-weeks of combined exercise could not be determined because the concentrations were below the detectable range.

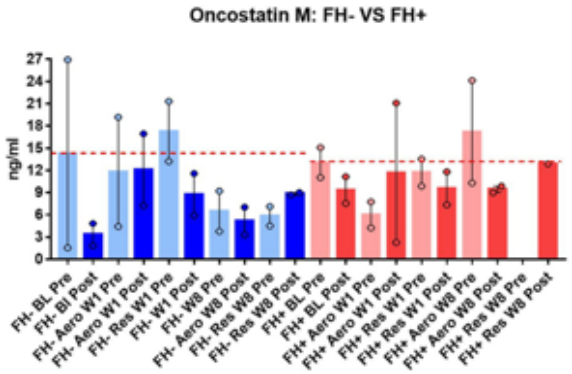

Figure 14. Regulatory effects of exercise on OSM after 8 weeks of combined exercise training.

Chapter 4: Discussion

Given that the prevalence of T2D has more than doubled within the last 20 years (cdc.gov, 2017), a coherent understanding of factors contributing to the development of T2D is necessary to prevent/cure the disease. Additionally, Mexican-Americans are at a greater risk for developing T2D compared to non-Hispanic whites (CDC, 2016). The present study provides valuable insight and helps fill the gap in literature concerning the implications of FH+ in Mexican-Americans in regard to insulin resistance, metabolic flexibility and myokine concentrations compared to FH- individuals. To the best of our knowledge, this is the first study to report that young, normoglycemic Mexican-Americans with FH+ improved insulin sensitivity, body composition, and muscle strength after combined exercise training to the same extent as FH- individuals. The primary finding of this study is that following an 8-week combined exercise training intervention, exercise induced improvements in body composition, and insulin sensitivity were not impacted by a family history of T2D in young, healthy normoglycemic Mexican-American men. Furthermore, a comparable insulin sensitivity, metabolic flexibility, resting energy expenditure, substrate utilization, and body composition between FH- and FH+ indicates that no metabolic defects were present in a healthy, young, Mexican-American population. The present study is one of a few to investigate the insulin sensitizing effects of exercise in young FH- and FH+ Mexican-Americans [46, 87].

Insulin Sensitivity

In the current study insulin sensitivity was assessed using the gold standard method, the hyperinsulinemic-euglycemic clamp [85], to determine the effects of FH+ on insulin sensitivity in a normoglycemic, healthy young Mexican-American population. Several studies indicate a lower insulin sensitivity in FH+ compared to FH- [3-10, 12, 13, 15, 88-90] whereas some report no difference in insulin sensitivity between FH- and FH+ [11, 16, 91]. The majority of these studies measure insulin sensitivity by HOMA-IR [4, 6, 90] QUIKI [12], or OGTT [4, 5, 8-10, 13, 15, 89, 91] whereas some studies measured insulin sensitivity using the clamp [3, 7, 13, 15, 88]. Gulli et al., 1992 was one of three studies that measured Insulin sensitivity in the Mexican-American population and reported a lower in insulin sensitivity in the FH+ group compare to FH- measured by the clamp. Gulli et al., (1992) reported to have only included 2 males compared to 9 females in the FH+ group as well as only 1 male compared to 9 females in the FH- group. Similarly, Ryder et al., (2002) found that Mexican-Americans with a first degree family history of T2D possessed increased insulin resistance and a low disposition index, which can account for increased insulin secretion to compensate for decreased insulin sesitivity, and together can help predict the progression of insulin resistance to T2D. Further, Civitraese et al., (2004) utilized clamp method to assess insulin sensitivity in FH- and FH+ Mexican-Americans, determined that FH+ had a significantly decreased insulin sensitivity compared to the FH- group [88]. Similarly, Pratipanawatr et al., (2001), also assessed insulin sensitivity in FH- and FH+ Mexican-Americans and Caucasians through the clamp and demonstrated that FH+ subjects had decreased insulin sensitivity compared to the FH- group [89]. Gulli et al., (1992) demonstrated that FH+ in

Mexican-American individuals had significantly lower glucose disposal rates (GDR) during a two-step clamp performed at 20 and 40-mU/min^{-1}/m^2 to elicit plasma insulin levels approximately to half maximal stimulation of total glucose disposal [15]. Our findings do not align with those reported by Gulli et al., (1992). Gulli et al. focused on the Mexican-American population consisting of mainly females, whereas our study was also conducted in Mexican-Americans but only examined the male population. As described by Kennedy et al., (1997), gender based differences such as insulin sensitivity may have been impacted by the lopsided number of male vs female subjects. Given that Insulin sensitivity is altered by different stages of the menstrual cycle and that contraceptives have shown to impact Insulin sensitivity negatively, the use of only male subjects will yield data that is not influenced by fluctuating hormone levels [90]. Gender based differences may have contributed towards difference in study outcomes [91]. Additionally, the FH+ group studied by Gulli et al., (1992) was on average older than the FH+ group in our study. As described by Pick et al., 1998, chronic hyperglycemia may lead to compensatory over secretion of insulin to enhance glucose uptake, which in turn is one of the hallmarks of insulin resistance. Therefore, older individuals may have a longer amount of time in the hyperglycemic state thus exacerbating insulin resistance. Our results suggest that insulin sensitivity is not impacted by a family history of T2D in young Mexican-American males. Our findings are in line with those of Ukropcova et al., (2007) who investigated the impact of FH+ in Caucasians, African-Americans, and Asians as well as findings from Heilbronn et al., (2007), who investigated the impact of FH+ in Caucasians [11]. Similar to our study, Ukropcova et al., (2007) measured insulin sensitivity by hyperinsulinemic-euglycemic

clamp and reported no difference in insulin sensitivity between FH- and FH+ in their target population of young Caucasians, African-Americans, and Asians. Similarly, Heilbronn et al., (2007) also assessed insulin sensitivity using the hyperinsulinemic-euglycemic clamp and reported no difference in insulin sensitivity between FH- and FH+. Moreover, our study used a much greater dose of insulin infusion (80 mu/min/m^2) for greater suppression of hepatic glucose production during the hyperinsulinemic-euglycemic clamp [85]. Key reasons for the disparities in the literature to the results of our study can be explained by several factors. First, the insulin signaling cascade may take a longer time to be disrupted by chronically elevated levels of blood glucose which will increase insulin secretion by the β-cells of the pancreas [92]. Over time these increased levels of circulating insulin combined with the negative feedback loop, may lead to disturbances of IRS-1 receptors on the cell which have been shown to impact glucose homeostasis [89, 93] Secondly, given that insulin resistance is partly driven by diminished β cell function, a consequence of chronic hyperglycemia, middle aged individuals, such as those studied by Pratipanawatr et al., (2001), Civitarese et al., (2004), and Gulli et al., (1992) may have had more time to exhaust the β cells of the pancreas as they aged [92]. Younger individuals regardless of Family history if T2D may not have had an ample amount of time in the hyperglycemic state to exacerbate IR. Furthermore, elevated levels of blood glucose over extended periods of time, can lead to high compensatory rates of insulin secretion by the pancreas which can lead to β-cell failure [15, 94]. While insulin sensitivity appears to be altered following exercise training, this effect may be altered in those with a family history of T2D and requires further exploration to fill gaps in the literature.

Exercise Induced Improvements

The insulin sensitizing effects of exercise have been studied extensively in healthy, obese, T2D and, FH+ individuals [18, 40, 48, 49, 95, 96]. Given that skeletal muscle comprises ~40% of total body mass in humans, skeletal muscle mass possesses a major role in glucose metabolism and insulin action. Skeletal muscle is regarded as the main tissue responsible for peripheral glucose disposal during an oral glucose tolerance test, hyperinsulinemic-euglycemic clamp as well during exercise [85]. After 8-weeks of combined exercise training, both groups improved insulin sensitivity. Given that a significant increase in muscle mass was evident in both groups, and that skeletal muscle plays a major regulatory role in glucose metabolism, higher GDR values accompanied by an increase in muscle mass may have made full use of their symbiotic relationship to enhance insulin sensitivity after exercise training [58, 60]. To account for the influence of increased muscle mass on insulin sensitivity, GDR was normalized by lean mass. After GDR normalization, our findings demonstrate that 8-weeks of combined exercise training was effective and can be used as a means to improve whole body insulin sensitivity. In a similar study that implemented 12 weeks of combined exercise training in a healthy population as well as patients with T2D, Meex et al., (2010) demonstrated a significant improvement in insulin sensitivity in T2D subjects [18]. Furthermore, in line with our findings in FH+ individuals, Jorge et al., (2011), demonstrated that T2D individuals were also able to achieve significant improvements in insulin sensitivity following 12 weeks of combined exercise training. A 6-month exercise intervention conducted by Wing et al., (1998), reported that individuals with FH+ significantly decreased body weight, BMI, fasting plasma glucose, and insulin.

These findings suggest that both T2D individuals as well as FH+ individual are able to reap the benefits of exercise after 8 weeks, 12 weeks, and 6 months of exercise training, respectively. The multifaceted novelty of our study includes the meals participants were provided with to control for diet in order to diminish the dietary effects of high fat/carbohydrate consumption on insulin sensitivity. Further, to the best of our knowledge, this is the first study to investgate the insulin sensitizing effects of combined exercise training on FH- and FH+ healthy, young Mexican-Amercians.

Exercise Induced Effects on Metabolic Flexibility

Considerable data indicates that FH+ and T2yjD individuals' exhibit diminished metabolic flexibility during insulin stimulated conditions [7, 15, 17-19]. In support, findings by Kelley et al., (2000), have shown that insulin-resistant skeletal muscle of young to middle aged participants with T2D is characterized by diminished metabolic flexibility. A study by Felber et al., (1987) demonstrated that obese and T2D subjects do not suppress lipid oxidation during the insulin stimulated state of the clamp compared to the normoglycemic control group. Additionally, Felber et al., (1987)., found that the 3 obese groups which were composed of individuals with normal glucose tolerance, Impaired glucose tolerance, and type 2 diabetes, displayed lower levels of glucose oxidation during an OGTT and clamp, indicating a higher oxidation of lipid compare to the normoglycemic subjects. Our data indicate, that there were no differences in metabolic flexibility between normoglycemic FH- and FH+ groups. In addition, there was no difference between groups in terms of change in metabolic flexibility from pre to post exercise intervention. In a similar study, Gulli et al., (1992) assessed metabolic flexibility

in FH- and FH+ Mexican-American during a two-step clamp and reported metabolic inflexibility in FH+ compared to FH-. Furthermore, Menshicova et al., (2007), conducted a 16-week study in which obese and lean endurance trained participants exercised aerobically for 30 minutes between 60-75% of VO_2max. Sixteen weeks of exercise intervention increased fasting fat oxidation as well as suppression of fat oxidation during the insulin stimulated state of the hyperinsulinemic euglycemic clamp, indicating an improvement of metabolic flexibility [97]. In the current study, metabolic flexibility was assessed at baseline and after 8-weeks of combined exercise training through indirect calorimetry during fasted conditions and insulin stimulated conditions. Our findings do not support data reported by Gulli et al., (1994) showing that metabolic flexibility is impacted by a family history of T2D. Again, the explanation to why our data do not align with that of Gulli et al., (1994), may be that on average, our Mexican-American subjects were relatively younger and may already have a healthy metabolic flexibility. We demonstrated that FH- and FH+ individuals had virtually identical RQ values during fasted conditions and insulin stimulated conditions at baseline while metabolic flexibility did not improve in either group after 8-weeks of combined exercise training. Furthermore, RMR data obtained during the clamp indicated that there was no statistically significant increase in caloric expenditure in either group from baseline to after 8-weeks of combined exercise training. Given that our data indicates that subjects in both groups had relatively normal RQ values (~0.70) at baseline and that both groups responded to the insulin stimulation to the same extent, our subjects may have had healthy/unimpaired metabolic flexibility. Therefore, there may have been minimal room for improvement in their already healthy relatively low RQ [18, 98].

Performance Enhancing Effects

The performance enhancing effects of combined exercise training have been previously reported [51, 99]. A 13-week resistance, aerobic, and combined exercise training study conducted by Glowacki et al., (2004), found that on average, upper body strength measured through 1RM bench press increased 7.5%, 30.5%, and 21.2% in the aerobic, resistance and combined exercise training groups, respectively. The exercise intervention also elicited improvement in lower-body strength with 1RM leg press by 20.4%, 40.8%, and 39.4% in the aerobic, resistance, and combined exercise training groups, respectively [99]. Additionally, absolute maximal aerobic capacity increased two-fold in the aerobic training group (~8%) compared to the resistance (3.7%) and combined exercise training groups (2.8%) [99]. Further, a study conducted by Tokmakidis et al (2004) which included combined resistance and aerobic exercise, demonstrated that both upper and lower body strength significantly increased after 4 and 16 weeks. Although our exercise intervention was 8-weeks in duration, we were able to achieve comparable improvements in upper and lower body strength and maximal aerobic capacity to that of Glowacki et al (2004). FH- and FH+ subjects in the current study improved upper-body strength measured by 1RM bench press 19.28% and 22.59%, respectively, while lower-body strength measured using a leg strength dynamometer improved in both FH- and FH+ groups 21.95% and 19.36%, respectively. In regard to improvements in absolute maximal aerobic capacity, the FH- group improved 4.4% and the FH+ group improved 7.4% after 8-weeks of exercise training. To the best of our knowledge, our data is the first to indicate that FH+ did not impact exercise mediated improvements in upper and lower body muscular strength.

Studies that investigate improvements in maximal aerobic capacity within individuals with FH+ are limited. Leite et al., (2009), conducted a study that included at risk individuals for T2D with FH+ who had hypertension, hyperinsulinemia, obesity, impaired glucose tolerance, and dyslipidemia but not T2D. These individuals underwent a maximal aerobic capacity exercise test and the most prevalent anomaly in the at risk FH+ group was a diminished maximal aerobic capacity [100]. It was reported that a lower VO_2max significantly correlated with impaired insulin sensitivity [100]. Contrary to Leite et al., (2009), our results indicated that FH- and FH+ had comparable absolute and relative VO_2max at baseline. In addition, although the FH+ group displayed an increase in VO_2max, the percent change improvement in VO_2max was also comparable between groups, indicating FH+ was not a limiting factor in exercise induced improvements in aerobic capacity within our study. The conflict of findings can be the difference in the mean age of our study participants being much younger compared to those reported in Leite et al (2009). Furthermore, a compromised lipid oxidation, such as that evident in those with metabolic diseases may also contribute to a diminished VO_2max ([18]. In our study defects in lipid oxidation were not evident. Further, we were able to show that there were no differences in lipid oxidation between the FH- and FH+ groups. Our findings also help gain a better understanding of combined exercise prescription necessary to help individuals yield improvements in maximal aerobic capacity.

Improvements in Body Composition

Combined exercise training has previously been reported to be effective in improving body composition [38, 45, 47]. Lucotti et al., (2011), incorporated a 3-week, aerobic (15-minute row ergometer & 15 minute of bicycle ergometer) and combined (5 upper-body and 4 lower-body exercises) exercise training intervention that included an aerobic training group and a combined exercise training group. Decreases in body weight and fat mass were reported in both groups after the 3-week exercise intervention [38]. Similarly, Tan et al., (2012) reported that T2D subjects who participated in a 6-month combined exercise training program significantly decreased their body fat percentage compared to the control group which did not exercise. In line with our study, Van Der Heijden et al., (2010) reported that after a 10-week resistance exercise program subjects significantly increased FFM. Our results show that both FH- and FH+ groups had virtually identical body composition values in terms of body weight and body fat %. Additionally, the FH- group significnaly increased body weight and had a significantly higher increase in body weight (delta) compared to the FH+ group after combined exercise training. Furthermore, we show that combined exercise training elicited an increase in FFM in both groups following 8-weeks of combined exercise training. To the best of our knowledge this is the first study to report that a family history of T2D does not impact exercise induced gains in FFM and strength.

Effects of Exercise on Myokines

Our exploratory aim, which investigated the effects of exercise on circulating concentrations of myokines and cytokines before and after acute bouts of aerobic, resistance exercise, and after 8-weeks of combined exercise training between FH- and FH+ individuals helps shed light on potential beneficial effects of combined exercise training. Given that the current study pooled plasma samples, statistical testing was not feasible and was not carried out. Our findings indicate that after 8-weeks of combined exercise training circulating IL-6 appears to have been downregulated in the FH- group which displayed varying concentrations in circulating IL-6 post intervention, while IL-6 concentration in the FH+ remained stagnant. Although we did not measure transcript variants, Oberbach et al., (2008) found that after 12 months of exercise the 174G/C variant in the IL-6 gene, which is responsible for IL-6 transcription, significantly reduced IL-6 serum concentrations [101]. Conversely, Kim et al., (2014), conducted a study incorporating combined exercise training 3 times per week for 12 weeks and found that when compared to the aerobic exercise training group the individuals partaking in combined exercise had a significantly lower serum IL-6 concentrations. While IL-6 appears to be altered following exercise training, this effect may be altered in those with a family history of T2D and requires further exploration.

Pooled serum IL-8 concentrations were shown to have been potentially regulated in the FH- and FH+ groups after 8 weeks of combined exercise training. As previously shown by Troseid et al., (2009), IL-8 was demonstrated to be significantly reduced after 8 weeks of combined aerobic and resistance exercise training and accompanied by

significant improvements in maximal aerobic capacity [102]. IL-8 is known to aid in the promotion of angiogenesis and could serve as a possible explanation to the improvements in maximal aerobic capacity by improving circulation and subsequently oxygen delivery to working muscles observed in our participants [103]. While the acute bouts of exercise appear to cause alterations in IL-8 in FH+ individuals and is also accompanied by similar improvements in delta and percent change aerobic capicty in both groups, there appears to be a possible divergence in circulating IL-8 between the groups. Such alterations in IL-8 release and signaling in FH+ individuals warrants further investigation.

OSM has shown to positively impact insulin resistance, fat mass, and glucose tolerance [104]. Our findings, which demonstrated a potential downregulation of OSM in the FH- and FH+ groups following 8-weeks of combined exercise align with the proposed effects of OSM reported by Komori et al., (2013). OSM concentrations may have been influenced by the combined exercise training intervention and improvements in insulin sensitivity which were observed in both FH- and FH+ groups. Furthermore, Komori et al., (2013), demonstrated that there was an inverse relationship between OSM and fasting insulin and AUC during an oral glucose tolerance test which does not align with our findings. Despite the regulatory effects of exercise on OSM after 8-weeks of combined exercise training, a significant decrease in glucose AUC after a 2-h OGTT test was observed in the FH+ group and a significant decrease in fasting insulin in the FH- group after 8-weeks of combined exercise training.

Circulating IL-15 concentrations were only obtained for the FH+ group at baseline (3.65 pg/ml). After exercise and collection, our blood samples were chilled on ice from 90-minutes (pre-exercise sample) to 15-minute (post-exercise samples). This variability in processing time may have influenced different myokines to degrade at different rates. Thus, providing an explanation to why some of our myokine assays detected ample amounts of myokine concentrations at different time points and others did not. Furthermore, given that IL-15 appears to be modified in the FH+ group following combined exercise training, this regulatory effect may be different than in FH- individuals and therefore requires further exploration.

According to Jackman et al., (2011), the age of the sample at the time of processing and freezing can impact the concentration of myokines. Additionally, future studies should consider employing high sensitivity kits, which are more susceptible to detect any changes or degradations in myokine concentrations compared to standard sensitivity kits that were used in our analyses.

Myostatin, a myokine known for its regulatory effects on lean muscle mass was only detected in the FH+ group, in which a robust regulatory effect was elicited following 8-weeks of combined exercise training. Our findings are in agreement with those of Kim et al., (2005), in which it was demonstrated that as little as 5 sessions of resistance training were effective in decreasing myostatin gene expression by 44%. Furthermore, Hittel et al., (2010), demonstrated that 6-months of aerobic training was effective in significantly decreasing circulating myostatin concentrations. Given that myostatin

appears to be modified in the FH+ group following 8 weeks of combined exercise training, this regulatory effect may be altered in those with a family history of T2D and requires further exploration.

Limitations

A limitation of our study can be the self-reported non-diabetic parental status in the FH- group, considering that about 25% of the diabetic population is undiagnosed (CDC, 2017). However, we have scrutinized this information to the best of our knowledge including confirmation with parents and when possible assessing fasting plasma glucose. Although all study participants received a controlled diet for 5 days prior to pre and post intervention testing, food consumption was not supervised. Given that higher amounts of dietary fat consumption alter insulin sensitivity [105], we cannot ignore the possibility of not fully adhering to the prescribed diet of all study participants. Lastly, the variable blood processing time may have influenced the results in regard to the exploratory aim and may help us understand optimal blood processing time and conditions to ensure that accurate results are derived.

Conclusion

In summary, we show that a family history of T2D does not impact exercise induced improvements in insulin sensitivity in young healthy Mexican-Americans. This supports the notion that exercise can serve as a powerful tool to combat insulin resistance, a precursor to T2D, regardless of a family history of T2D in young normoglycemic population. We also demonstrated that 8-weeks of combined exercise training is effective in improving upper and lower body strength, fat free mass, and body fat % regardless of a family history if T2D. Future studies should explore the mechanisms associated with insulin resistance in different age groups to account for the longer cumulative time older individuals have to exacerbate the disease by living in a chronic state of hyperglycemia and potentially paving the way to β cell exhaustion.

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Appendix A

Table 1. Literature Overview- Effects of Family History of Type 2 Diabetes on Insulin Sensitivity

Study	Status	Family History	Method	Outcome	Age	Sex	Race
Petersen et al. 2004	Insulin Resistant & Insulin Sensitive	One parent or grandparent	Hyperinsulinemic-Euglycemic Clamp	↓ IS in FH+	25-29	8m/18F	NA
Perseghin et al. 1997	Normoglycemic	First-degree relative	Hyperinsulinemic euglycemic clamp	↓ IS in FH+	19-41	28M/50F	White
HeilBronn et al. 2007	Normoglycemic	First-degree relative	Hyperinsulinemic euglycemic clamp	No Difference	34-52	5M/12F	White
Arslanian et al. 2005	Normoglycemic	First-degree relative	Hyperinsulinemic euglycemic clamp	↓ IS in FH+	11-12	25M/29F	White
Groop et al. 1996	Normoglycemic	First-degree relative	Hyperinsulinemic euglycemic clamp & OGTT	↓Glucose tolerance in FH+ ↓ IS in FH+	35-65	46M/39F	Hispanic
Gulli et al. 1992	Normoglycemic	First-degree relative	Hyperinsulinemic euglycemic clamp & OGTT	No Difference in OGTT ↓ IS in FH+	34-42	3M/18F	Mexican-American
Van Haeften et al. 1998	Normoglycemic	First-degree relative	Hyperglycemic clamp & OGTT	No Difference	44-47	8M/34F	White
Haffner et al. 1997	Normoglycemic & Impaired Glucose Tolerance	First-degree relative	2-h OGTT	↓Glucose tolerance in FH+	25-65	533M/743F	Hispanics & African Americans
Ishikawa et al. 1998	Normoglycemic	First-degree relative	2-h OGTT	↓ IS in FH+	26-52	52M/36F	White
Ramachandran et al. 1997	Normoglycemic & Impaired Glucose Tolerance	First-degree relative	2-h OGTT	↓Glucose tolerance in FH+	20+	810M/936F	Indian
Warram et al. 1990	Normoglycmic	First-degree relative	2-h OGTT	↓ IS in FH+	16-60	71M/84F	NA
Osei et al. 1991	Normoglycemic	Family history of diabetes	2-h OGTT FSIVGTT	↓ IS in FH+	24-30	4M/16F	N/A
Wang et al. 2008	Normoglycemic & Impaired glucose tolerance & T2D	First-degree relative	2-h OGTT HOMA-IR	↓Glucose tolerance in FH+	31-65	183M/240F	Chinese
Ryder et al. 2003	Normoglycemic	Relatives with diabetes	HOMA-IR	↓ IS in FH+	18-68	66M/77F	Hispanic
Guerrero et al. 2005	Normoglycemic	Family history of diabetes	HOMA-IR	↓ IS in FH+	18-24	18M/30F	White
Perez-Fuentes et al. 2014	Normoglycemic	First-degree relative	QUICKI	↓ IS in FH+	18-65	602 M&F	White

Appendix B

Table 2. Literature Overview- Effects of family history of type 2 diabetes on insulin sensitivity – sorted for Insulin Sensitivity Methodology

Author	Status	Method	Outcome FH+ vs. FH-	Age	Sex	Race
Arslanian et al. 2005	Normoglycemic	Hyperinsulinemic euglycemic clamp	↓ IS in FH+	11-12	25M/29F	White
Petersen et al. 2004	Insulin resistant & Insulin sensitive	Hyperinsulinemic euglycemic clamp	↓ IS in FH+	19-36	8M/18F	Black White
Perseghin et al. 1997	Normoglycemic	Hyperinsulinemic euglycemic clamp	↓ IS in FH+	19-41	28M/50F	Mexican
Groop et al. 1996	Normoglycemic	OGTT Hyperinsulinemic euglycemic clamp	↓Glucose tolerance in FH+ ↓ IS in FH+	35-65	46M/39F	Hispanic
Gulli et al. 1992	Normoglycemic	OGTT Hyperinsulinemic euglycemic clamp	No Difference in OGTT	34-42	3M/18F	Mexican-American
Van Haeften et al. 1998	Normoglycemic	OGTT & Hyperglycemic clamp	↓ IS in FH+ No Difference	44-47	8M/34F	White
Wang et al. 2008	Normoglycemic	2-h OGTT	↓Glucose tolerance in FH+	31-65	183M/240F	Chinese
Ishikawa et al. 1998	Normoglycemic	2-h OGTT	↓Glucose tolerance in FH+	26-52	52M/36F	White
Haffner et al. 1997	Normoglycemic	2-h OGTT	↓Glucose tolerance in FH+	25-65	533M/743F	Hispanics & African Americans
Osei et al. 1991	Normoglycemic	2-h OGTT FSIVGTT	↓ IS in FH+	24-30	4M/16F	N/A
Ryder et al. 2003	Normoglycemic	HOMA-IR	↓ IS in FH+	18-68	66M/77F	Hispanic
Guerrero et al. 2005	Normoglycemic	HOMA-IR	↓ IS in FH+	18-24	18M/30F	White
Perez-Fuentes et al. 2014	Normoglycemic	QUICKI	↓ IS in FH+	18-65	602 M&F	White

Table 2. Literature Overview- Effects of family history of type 2 diabetes on insulin sensitivity – sorted for Insulin Sensitivity Methodology

Author	Status	Method	Outcome FH+ vs. FH-	Age	Sex	Race
Arslanian et al. 2005	Normoglycemic	Hyperinsulinemic euglycemic clamp	↓ IS in FH+	11-12	25M/29F	White
Petersen et al. 2004	Insulin resistant & Insulin sensitive	Hyperinsulinemic euglycemic clamp	↓ IS in FH+	19-36	8M/18F	Black White
Perseghin et al. 1997	Normoglycemic	Hyperinsulinemic euglycemic clamp	↓ IS in FH+	19-41	28M/50F	Mexican
Groop et al. 1996	Normoglycemic	OGTT Hyperinsulinemic euglycemic clamp	↓Glucose tolerance in FH+ ↓ IS in FH+	35-65	46M/39F	Hispanic
Gulli et al. 1992	Normoglycemic	OGTT Hyperinsulinemic euglycemic clamp	No Difference in OGTT ↓ IS in FH+	34-42	3M/18F	Mexican-American
Van Haeften et al. 1998	Normoglycemic	OGTT & Hyperglycemic clamp	No Difference	44-47	8M/34F	White
Wang et al. 2008	Normoglycemic	2-h OGTT	↓Glucose tolerance in FH+	31-65	183M/240F	Chinese
Ishikawa et al. 1998	Normoglycemic	2-h OGTT	↓Glucose tolerance in FH+	26-52	52M/36F	White
Haffner et al. 1997	Normoglycemic	2-h OGTT	↓Glucose tolerance in FH+	25-65	533M/743F	Hispanics & African Americans
Osei et al. 1991	Normoglycemic	2-h OGTT FSIVGTT	↓ IS in FH+	24-30	4M/16F	N/A
Ryder et al. 2003	Normoglycemic	HOMA-IR	↓ IS in FH+	18-68	66M/77F	Hispanic
Guerrero et al. 2005	Normoglycemic	HOMA-IR	↓ IS in FH+	18-24	18M/30F	White
Perez-Fuentes et al. 2014	Normoglycemic	QUICKI	↓ IS in FH+	18-65	602 M&F	White

Appendix C

Phone Interview

1. Male?

2. How would you describe your mother's ethnicity?

3. How would you describe your father's ethnicity?

4. What is your age?

   Age: 18 ≤ Age ≤ 40 years? YES NO
   DOB:

5. To your knowledge, how would your fasting blood glucose be classified?

   LOW NORMAL HIGH

   Comments:

6. What is your height? _____cm

7. What is your weight? _____kg

8. (Tester calculate BMI) 18 ≤ BMI ≤ 30 kg/m^2

9. To your knowledge, how would your blood pressure be classified?

   LOW NORMAL HIGH

   Can you provide an estimated value? _____

10. Do your parents have Type 2 Diabetes? (none, one parent, or both parents)

    If so, which parent?

11. Do you exercise regularly? YES NO
    Explain what type of exercise you perform and how many minutes per week you spend doing these exercises.
12. Hyperlipidemia

To your knowledge, do you have high cholesterol? YES NO

To your knowledge, do you have high triglycerides? YES NO

Comments:

13. Do you have any medical conditions or illnesses? YES NO

Comments:

14. Are you currently taking any medications? YES NO

If so, what are they for?

15. To your knowledge, has there been evidence supporting that you may have cardiovascular disease or diabetes? YES NO

Comments:

16. Are you currently taking any drugs that may affect your energy metabolism and body weight? YES NO

Comments:

17. Describe the frequency in which you:

1. Consume alcohol:
2. Use recreational drugs:
3. Smoke cigarettes or e-cigarettes:
4. Use chewing tobacco:

Comments:

5. Do you currently have any type of eating disorder or eating attitudes that may interfere with the study? YES NO

Comments:

Pass or Fail

Comments:

Date & Time for Obtaining Signed Consent _____

**Be sure to inform subject that they need to come FASTING when signing the consent form*

Accelerometer Applied _____

Accelerometer Removed _____

Accelerometer #: _____

Appendix D

1Repetition Maximum Protocol- HITD

1. General Warm up for 5 minutes on treadmill- Slow paced jog.
2. Shoulder joint warm up. Arm circles forwards (20) & backwards (20).
3. 20 horizontal arm abduction to adduction.

Specific warm up: Practice correct form execution with barbell.

1. Grip bar slightly wider than shoulder grip to ensure that forearms are perpendicular to the ground once barbell is in contact with the chest at the lowered position.
1. 5 points of contact at all times
    1. 2 feet
    2. Buttocks
    3. Back
    4. Head
2. ALWAYS PRACTICE PROPER SPOTING TECHNIQUE

Bench press warm up sets

_____ 40% of self-predicted 1 RM - 8 repetitions, 2-minute rest

_____ 50% - 5 repetitions, 2-minute rest

_____ 60% - 3 repetitions, 3-minute rest

Working set to 1Repetition Maximum

_____ 80% - 1 repetition, 3-minute rest

_____ 90% - 1 repetition, 3-minute rest

_____ 100% - 1 repetition, 4-minute rest

_____ 105% - 1 repetition

Back leg strength dynamometer

Warm up

1. 15 jumping jacks
2. Above the knee barbell deadlift pulls
3. 2 practice pulls not to maximal effort

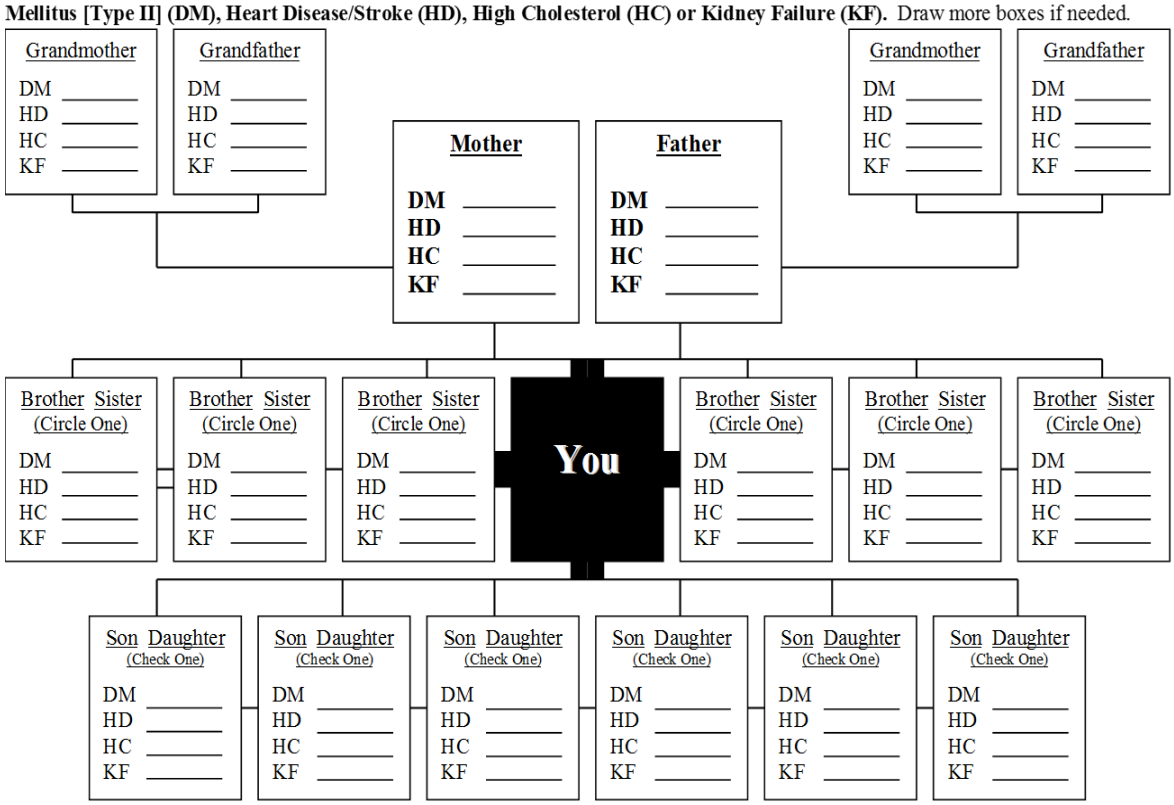
_____ attempt 1, 3-minute rest

_____ attempt 2, 3-minute rest

_____ attempt 3, 3-minute rest

Appendix E
Family History of Illness/ Disease

Researcher: Please review with the participants the number of siblings they have. Include all described relatives related by blood. For example ½ siblings would be related by blood. Step or adopted siblings would not be included. Write in box if the participant's relative has/had **Diabetes Mellitus [Type II] (DM), Heart Disease/Stroke (HD), High Cholesterol (HC) or Kidney Failure (KF).** Draw more boxes if needed.



If none of the participant's relatives have any of these conditions check here ☐

Researcher signature _____ Date _____

Appendix F

Food Allergies

Please mark with an X if you are allergic to or if you dislike any of the following foods and/or food components					
FOOD	Allergic	Dislike	FOOD	Allergic	Dislike
Apples			White rice		
Avocados			Tortilla (corn)		
Bananas			Corn taco shell		
Melon (Cantaloupe)			Flat whole wheat bread		
Melon (Watermelon)			Whole wheat cereal		
Strawberries			Eggs		
Carrots medium			Low fat beef mince		
Carrots small			Chicken breast fillet		
Garlic			Margarine		
Lettuce shredded			Peanut oil		
Lettuce torn leaves			Milk 2% fat		
Mushrooms medium			Cheddar cheese		
Onions			Ice cream		
Tomatoes cherry			Ground cinnamon		
Tomatoes			Balsamic vinegar		
Capsicum (Red bell peppers)			Seasoning mix, chili-based for tacos		
Chili red			Oyster sauce		
Rolled oats raw			Honey		
Mixed grain bread			Vegetarian refried bean (tomato, cumin, garlic, chili powder)		
Water			Other		

Appendix G

Body Composition / Anthropometry

DOB:	AGE:				
	Trial 1	Trial 2	Trial 3	Average	Initials
Weight (kg)					
Height (cm)					
BMI (kg/m2)					
Waist (cm)					
Hips (cm)					
WHR (cm)					
Bod Pod					
Total body weight (kg)					
Fat mass (kg)					
Lean mass (kg)					
Body fat %					
DXA					
Total body weight (kg)					
Fat mass (kg)					
Lean mass (kg)					
Body fat %					
Bone mineral density					

Comments: _____

Body Composition / Anthropometry

Measurement Units	Formula and Calculation
Kilograms and meters (or centimeters)	Formula: weight (kg) / [height (m)]^2 With the metric system, the formula for BMI is weight in kilograms divided by height in meters squared. Because height is commonly measured in centimeters, divide height in centimeters by 100 to obtain height in meters. Example: Weight = 68 kg, Height = 165 cm (1.65 m) Calculation: 68 ÷ (1.65)^2 = 24.98
Pounds and inches	Formula: weight (lb) / [height (in)]^2 x 703 Calculate BMI by dividing weight in pounds (lbs) by height in inches (in) squared and multiplying by a conversion factor of 703. Example: Weight = 150 lbs, Height = 5’5” (65”) Calculation: [150 ÷ (65)^2] x 703 = 24.96

Appendix H

Physical Activity Recall questionnaire

Today's Date _____ Day (circle one): Mon Tues Wed Thurs Fri Sat Sun

1. Were you employed in the last seven days? 0. No (Skip to Q#3) 1. Yes
2. If yes, which days? Mon Tues Wed Thurs Fri Sat Sun
3. What two days do you consider your weekend days? Mon Tues Wed Thurs Fri Sat Sun

		DAYS						
		1	2	3	4	5	6	7
Day: (mm/dd/yy)								
Date:								
Sleep: In Bed / Up Total time								
Work: Start / End Total time		Moderate						
MORNING	Hard							
	Very Hard							
	Moderate							
AFTERNOON	Hard							
	Very Hard							
	Moderate							
EVENING	Hard							
	Very Hard							

PAR Questionnaire – Page 2

4. Compared to your physical activity over the past three months, was last week's physical activity more, less or about the same?
   1. More 2. Less 3. About the same

KEY	Rounding:	10-22 min = 0.25 hr
Place asterisk (*) to the right of a work-related activity & the time spent doing it.		23-37 min = 0.50 hr 38-52 min = 0.75 hr 53-1:07 hr:min = 1.0 hr 1:08-1:22 hr:min = 1.25 hr

INTERVIEWER:
Please answer questions below and note any comments on interview.

5. Were there any problems with the 7-Day PAR interview? 0. No
   1. Yes (If yes, please explain.)

6. Do you think this was a valid 7-Day PAR interview? 0. No (Please explain)
   1. Yes

1. Please list below any activities reported by the subject that you don't know how to classify.

8. Please provide any other comments you may have in the space below.

SEVEN-DAY PHYSICAL ACTIVITY RECALL (PAR) LIST OF ACTIVITIES

Intensity	Job	Home	Sport or Recreation
LIGHT	* Typing * Standing * Driving	* Ironing, sewing * Light auto repair * Indoor Painting	* Leisurely walking * Softball * Bowling * Playing a musical instrument
MODERATE (easy effort)	* Lifting or carrying light objects (up to 5 lbs) * Painting out-side of house	* Sweeping, Mopping, Vacuuming * Clipping hedges * Raking * Mowing lawn with power mower * Cleaning windows	* Brisk walking (on level ground) * Shooting baskets * Throwing frisbee * Cycling leisurely on level ground * Swimming laps * Weightlifting

		* Pushing stroller with child	
	* Construction work (uphill)	* Scrubbing floors	* Brisk walking
	* Lifting or carrying objects (5-15 lbs)	* Shoveling dirt, coal, etc. * Mowing lawn with non-power mower	* Backpacking (on level ground) * Brisk cycling on level ground without losing breath
HARD	* Climbing ladder or stairs (moderate	* Carrying child (5-15 lbs)	* Tennis (doubles) * Downhill skiing * Swimming laps effort)
	* Carrying heavy loads such as bricks or lumber * Carrying moderate loads upstairs (16-40 lbs)	* Digging ditches * Chopping or splitting wood * Gardening with heavy tools	* Jogging * Basketball (in game) * Soccer (in game) * Backpacking (uphill) * Cycling (uphill or racing) * Tennis (singles) * Cross-country skiing * Swimming laps (hard effort) * Aerobic dancing * Circuit training (using a series of Nautilus machines without stopping)
VERY HARD			

Appendix I

Accelerometer Instructions

1. Put the accelerometer on using the elastic band and make sure it is close to your hip bone.
2. Ensure the monitor is worn upright (the black circular cap should be on top).
3. Ensure the monitor is worn on the RIGHT side of the body.
4. Wear the unit day and night until the scheduled return date.
5. Use caution when undressing to avoid dropping the unit on the floor.
6. **Do not expose to water or extreme temperatures.**
7. Remove it only to bathe or shower (place unit on your towel to remind you to reapply it immediately after dressing).
8. Avoid swimming during your scheduled time to wear the unit. If swimming would normally be a significant part of your activity during this period notify the staff of this fact.
9. Please DO NOT lose it.
10. Wear the unit until your next visit.

Appendix J

5 Day Menu- Dietary meal plan
McAinch & Bajpeyi
10500kj or 2500kcal

Gender , Age (years), Weight (kg), Height (cm), Sedentary Activity

Day	Meal	Food	Quantity	Note
Day 1				
	Breakfast			
		Oats,rolled,raw	80g	1 cup
		Milk,cow,fluid,reduced fat (~1.5%),increased calcium,added vitamins A & D	480 mL	2 cups
		Banana,cavendish,peeled,raw	1 medium (12-17cm long)	
		Cinnamon,ground	1 tsp	
	lunch			
		Bread,from wholemeal flour,added fibre	4 slice	
		Lettuce,cos,raw	0.25 cup (shredded/chopped)	
		Tomato,common,raw	1.5 medium (6-8cm dia)	Sliced circularly
		Cheese,cheddar,reduced fat (~ 25%)	1.65 slice (pre packed)	1/2 cup
		Mushroom,common,raw	4 medium	Sliced vertically
		Carrot,mature,peeled,raw	1 medium (17cm long)	Shreded for salad
		Margarine spread,polyunsaturated (70% fat),sodium = 360 mg/100 g,added vitamin E	26g	2 tbsp
		Capsicum,red,raw	0.5 medium Sliced	
	dinner			
		Vegetarian refried beans	1 Serveing (1 CUP)	
		Tortilla,from corn flour	1 Medium (~15cm dia)	
		Rice,white,boiled without added salt	1 cup (cooked)	
		Tomato,common,raw	1.5 medium (6-8cm dia) Sliced circularly	
		Lettuce,cos,raw	0.5 cup (torn leaves)	

	Avocado,hass,raw	0.25 avocado	
	Vinegar	1 tb	
	Capsicum,red,raw	0.5 medium	Sliced vertically
	Carrot,mature,peeled,raw	1 small (14cm long)	Shredded for salad
	Margarine spread,polyunsaturated (70% fat),sodium = 360 mg/100 g,added vitamin E	19g	1.5 tbsp
snack			
	Melon,watermelon,peeled,raw	300g	Cut to 1” squares
	Strawberry,fresh,raw	100g	Remove stem
	Melon,rockmelon (cantaloupe),peeled,raw	100g	Cut to 1” squares
	Ice cream,reduced fat,vanilla & other non-chocolate flavours	1 cup	
	Banana,cavendish,peeled,raw	1 medium (12-17cm long)	
	Water,tap	1.5 L	
	Apple,granny smith,unpeeled,raw	1 apple	

Day 2			
Breakfast			
	Oats,rolled,raw	80g	1 cup
	Milk,cow,fluid,reduced fat (~1.5%),increased calcium,added vitamins A & D	480 mL	2 cups
	Banana,cavendish,peeled,raw	1 medium (12-17cm long)	
	Honey	2.5 tb	
lunch			
	Vegetarian refried beans	1 Serve	
	Tortilla,from corn flour	56g	only 10mg sodium not 425mg but balanced out with other products
	Lettuce,cos,raw	0.25 cup (shredded/chopped)	
	Tomato,common,raw	1.5 medium (6-8cm dia)	Sliced
	Cheese,cheddar,reduced fat (~ 25%)	1.65 slice (pre packed)	1/2 cup
	Mushroom,common,raw	4 medium	Sliced
	Carrot,mature,peeled,raw	1 medium (17cm long)	Shreded
	Avocado,hass,raw	0.25 avocado	
	Margarine spread,polyunsaturated (70% fat),sodium = 360 mg/100 g,added vitamin E	19g	1.5 tbsp
	Egg,chicken,whole,raw	1 egg; large, Edible portion from 50 g egg	
	Capsicum,red,raw	0.5 medium	Sliced
dinner			
	Beef,mince,low fat,raw	56.7g	2 ounces
	Taco shell,from corn flour,plain	2 regular (12.5cm dia)	
	Onion,mature,peeled,raw,nfs	0.25 medium (6cm dia)	Sliced
	Seasoning mix,chilli-based,for tacos	5g	
	Tomato,common,raw	1.5 medium (6-8cm dia)	Sliced

	Lettuce,cos,raw	0.5 cup (torn leaves)	
	Capsicum,red,raw	0.5 medium	Sliced
	Carrot,mature,peeled,raw	1 small (14cm long)	
	Bread,flat (pita/lebanese style),wholemeal	86g	2 rolls
	Margarine spread,polyunsaturated (70% fat),sodium = 360 mg/100 g,added vitamin E	13g	1tbsp
snack			
	Melon,watermelon,peeled,raw	300g	Cut to 1” squares
	Strawberry,fresh,raw	150g	Remove stem
	Melon,rockmelon (cantaloupe),peeled,raw	100g	Cut to 1” squares
	Banana,cavendish,peeled,raw	1 medium (12-17cm long)	
	Water,tap	1.5 L	
	Apple,granny smith,unpeeled,raw	1 apple	

Day 3				
	Breakfast			
		Oats,rolled,raw	80g	1 cup
		Milk,cow,fluid,reduced fat (~1.5%),increased calcium,added vitamins A & D	480 mL	2 cups
		Banana,cavendish,peeled,raw	1 medium (12-17cm long)	
		Cinnamon,ground	1 tsp	
	lunch			
		Beef,mince,low fat,raw	56.7g	2 ounces
		Onion,mature,peeled,raw,nfs	0.25 medium (6cm dia)	Sliced
		Seasoning mix,chilli-based,for tacos	5g	
		Tomato,common,raw	1.5 medium (6-8cm dia)	Sliced
		Lettuce,cos,raw	0.5 cup (torn leaves)	
		Capsicum,red,raw	0.5 medium	Sliced
		Cheese,cheddar,reduced fat (~25%)	0.825 slice (pre packed)	1/4 cup
		Carrot,mature,peeled,raw	1 small (14cm long)	Shreded
		Bread,flat (pita/lebanese style),wholemeal	86g	2 rolls
		Margarine spread,polyunsaturated (70% fat),sodium = 360 mg/100 g,added vitamin E	26g	2tbsp
	dinner			
		Vegetarian refried beans	1 Serve	1 Cup
		Tortilla,from corn flour	56g	only 10mg sodium not 425mg but balanced out with other products
		Rice,white,boiled without added salt	1 cup (cooked)	
		Tomato,common,raw	1.5 medium (6-8cm dia)	Sliced
		Lettuce,cos,raw	0.5 cup (torn leaves)	

	Avocado,hass,raw	0.25 avocado	
	Vinegar	1 tb	
	Capsicum,red,raw	0.5 medium	Sliced
	Carrot,mature,peeled,raw	1 small (14cm long)	Shreded
	Margarine spread,polyunsaturated (70% fat),sodium = 360 mg/100 g,added vitamin E	26g	2tbsp
snack			
	Melon,watermelon,peeled,raw	300g	Cut to 1” squares
	Strawberry,fresh,raw	100g	Remove stem
	Melon,rockmelon (cantaloupe),peeled,raw	200g	Cut to 1” squares
	Ice cream,reduced fat,vanilla & other non-chocolate flavours	0.66 cup	
	Banana,cavendish,peeled,raw	1 medium (12-17cm long)	
	Water,tap	1.5 L	
	Apple,granny smith,unpeeled,raw	1 apple	

Day 4			
Breakfast			
	Oats,rolled,raw	80g	1 cup
	Milk,cow,fluid,reduced fat (~1.5%),increased calcium,added vitamins A & D	480 mL	2 cups
	Banana,cavendish,peeled,raw	1 medium (12-17cm long)	
	Honey	1 tb	
lunch			
	Bread,from wholemeal flour,added fibre	4 slice	
	Lettuce,cos,raw	0.25 cup (shredded/chopped)	
	Tomato,common,raw	1.5 medium (6-8cm dia)	
	Cheese,cheddar,reduced fat (~ 25%)	1.65 slice (pre packed)	1/2 cup
	Mushroom,common,raw	4 medium	Sliced
	Carrot,mature,peeled,raw	1 medium (17cm long)	Shreded
	Margarine spread,polyunsaturated (70% fat),sodium = 360 mg/100 g,added vitamin E	26g	2tbsp
	Egg,chicken,whole,raw	1 egg; large, Edible portion from 50 g egg	
dinner			
	Beef,mince,low fat,raw	56.7g	2 ounces
	Taco shell,from corn flour,plain	2 regular (12.5cm dia)	
	Onion,mature,peeled,raw,nfs	0.25 medium (6cm dia)	Sliced
	Seasoning mix,chilli-based,for tacos	5g	
	Tomato,cherry,raw	1 cup (cherry tomato)	
	Lettuce,cos,raw	0.5 cup (torn leaves)	
	Capsicum,red,raw	1 medium	Sliced
	Carrot,mature,peeled,raw	1 small (14cm long)	Shreded
	Bread,flat (pita/lebanese style),wholemeal	86g	2 rolls

	Margarine spread,polyunsaturated (70% fat),sodium = 360 mg/100 g,added vitamin E	26g	2tbsp
snack			
	Melon,watermelon,peeled,raw	300g	Cut to 1” squares
	Strawberry,fresh,raw	150g	Remove stem
	Melon,rockmelon (cantaloupe),peeled,raw	200g	Cut to 1” squares
	Banana,cavendish,peeled,raw	1 medium (12-17cm long)	
	Water,tap	1.5 L	
	Apple,granny smith,unpeeled,raw	1 apple	

Day 5			
Breakfast			
	Oats,rolled,raw	80g	1 cup
	Milk,cow,fluid,reduced fat (~1.5%),increased calcium,added vitamins A & D	480 mL	2 cups
	Banana,cavendish,peeled,raw	1 medium (12-17cm long)	
	Cinnamon,ground	1 tsp	
lunch			
	Bread,from wholemeal flour,added fibre	4 slice	
	Lettuce,cos,raw	0.25 cup (shredded/chopped)	
	Tomato,common,raw	1.5 medium (6-8cm dia)	Sliced
	Cheese,cheddar,reduced fat (~25%)	0.85 slice (pre packed)	1/4 cup
	Mushroom,common,raw	4 medium	Sliced
	Carrot,mature,peeled,raw	1 medium (17cm long)	Sliced
	Margarine spread,polyunsaturated (70% fat),sodium = 360 mg/100 g,added vitamin E	26g	2tbsp
dinner			
	Chicken,breast,lean,raw	0.5 fillet; yeild after skin and fat removed	
	Rice,white,boiled without added salt	1.5 cup (cooked)	
	Capsicum,red,raw	1 medium	Sliced
	Carrot,mature,peeled,raw	1 small (14cm long)	Shredded
	Onion,mature,peeled,raw,nfs	0.25 medium (6cm dia)	Sliced
	Mushroom,common,raw	4 medium	Sliced
	Chilli (chili),red,raw	2 chilli	Whole
	Sauce,oyster,Asian,commercial	3 tsp	In zip lock bag
	Garlic,peeled,raw	1 clove	
	Oil,peanut	2 tsp	
	Broccoli,fresh,raw	100g	
	Margarine spread,polyunsaturated (70%	26g	2tbsp

	fat),sodium = 360 mg/100 g,added vitamin E		
	Tomato,cherry,raw	1 cup (cherry tomato)	
snack			
	Melon,watermelon,peeled,raw	300g	Cut to 1” squares
	Strawberry,fresh,raw	100g	Remove stem
	Melon,rockmelon (cantaloupe),peeled,raw	200g	Cut to 1” squares
	Ice cream,reduced fat,vanilla & other non-chocolate flavours	0.5 cup	
	Banana,cavendish,peeled,raw	1 medium (12-17cm long)	
	Water,tap	1.5 L	
	Apple,granny smith,unpeeled,raw	1 apple	

Appendix K

VO_2 MAX

Weight (kg):		DOB:		Staff Initials:		
Height (cm):		Age Predicted Max HR (bpm)208-(0.7xage):				
Resting VO2 Values: L/min			ml/kg/min			
Stage	Time (min)	L/min	ml/kg/min	HR (bpm)		
Resting VO2	1					
	2					
	3					
	4					
	5					
Stage	Time (min)	Speed	Incline	HR (bpm)	RPE	VO2
Warm up	1	3.5 mph	3%			
Warm up	2	3.5 mph	3%			
Warm up	3	3.5 mph	3%			
	4	5 mph	0			
	5	5 mph	0			
	6		1%			
	7		2%			
	8		3%			
	9		4%			
	10		5%			
	11		6%			
	12		7%			
	13		8%			
	14		9%			
	15		10%			
	16		11%			
	17		12%			
	18		13%			
	19		14%			
	20		15%			
Recovery	1	3 mph	0			
Recovery	2	3 mph	0			
Recovery	3	3 mph	0			
Recovery	4	3 mph	0			
Recovery	5	3 mph	0			
VO2M:						
HRM:						

Vo2 Max Criteria	Achieved (Yes/No)	Value
Plateau reached		
Peak RER ≥ 1.1		
Max heart rate reached		
RPE ≥ 17		
Total number of criteria met		**/4**
VO2max achieved with a minimum of 2/4 criteria met (circle one)	**Yes**	**NO**

Appendix L

Oral Glucose Tolerance Test (OGTT)

Instructions:
1. Explain procedure to patient.
2. Take a blood sample and measure fasting glucose two times.
3. Give 75 grams of glucose drink.
4. Collect blood samples at indicated time intervals and record value two times.

Time frame	Time	Trail 1	Trial 2	Average
Fasting glucose				
15 minutes				
30 minutes				
60 minutes				
90 minutes				
120 minutes				
150 minutes				
180 minutes				

	A1C (percent)	Fasting Plasma Glucose (mg/dL)	Oral Glucose Tolerance Test (mg/dL)
Diabetes	6.5 or above	126 or above	200 or above
Prediabetes	5.7 to 6.4	100 to 125	140 to 199
Normal	About 5	99 or below	139 or below

Comments:

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Vita

Manuel Amador Jr. was born in El Paso TX. The second son of Manuel Amador and Elizabeth Reyes. Manuel graduated from Montwood High School in the spring of 2007. He enrolled at The University of Texas at El Paso in the fall of 2007 where he graduated with a bachelors in Science of Kinesiology. In the Fall of 2014 he began his masters in Science of Kinesiology. While working on his master's degree he worked as a teaching and research assistant for the department of kinesiology. Manuel was also employed as a Physical Therapy Technician at Highlands Rehabilitation Hospital throughout his graduate career. He has been a guest lecturer for both undergraduate and graduate kinesiology courses at UTEP as well as at El Paso Community College. In the Spring of 2017 & 2018, Manuel was an oral poster presentation finalist at the ACSM Texas chapter conference in Austin Texas, where he earned 3rd and 1st place in the state, respectively.

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Thesis was typed by Manuel Amador