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Metabolic rate and vascular function are reduced in women with a family history of type 2 diabetes mellitus

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Abstract

Metabolic and vascular abnormalities have been found in individuals with type 2 diabetes mellitus (T2D). Family history is often associated with increased risk of the development of T2D. We sought to determine if young, sedentary, insulin-sensitive individuals with a family history of T2D (FH+) have a reduced resting energy expenditure (REE) and vascular endothelial function compared with individuals who have no family history of T2D (FH−). The REE was determined in 18 FH+ individuals and 15 FH− individuals using indirect open-circuit calorimetry. Vascular endothelial function was measured via flow-mediated dilation (FMD) of the brachial artery. C-reactive protein and interleukin-6 were also measured to look at vascular inflammation. Body composition was measured via bioelectrical impedance analysis to determine fat-free mass and fat mass for each individual. Insulin resistance was calculated using the homeostasis model assessment equation and fasting insulin and glucose concentrations. Subjects (n = 42) were approximately 26 years old and had normal fasting serum insulin or glucose concentrations. The REE normalized for body weight (kilocalories per day per kilogram body weight) was significantly reduced in the FH+ women compared with FH− women ($P < .001$) but not in the men. The FMD was significantly reduced (34.3%) in the FH+ group compared with the FH− in women ($P = .002$). However, no between-group difference in FMD was present in male subjects ($P = .376$). Young, healthy, insulin-sensitive women with a family history of T2D have reduced whole-body metabolic rate and vascular endothelial function compared with those with no family history of disease. These differences in whole-body metabolic rate and vascular endothelial function were not present in male subjects.

1. Introduction

Individuals who have at least one parent with type 2 diabetes mellitus (T2D) have a 50% increased chance of developing T2D independent of other risk factors such as obesity and inactivity [1]. The development of T2D is often associated with environmental determinants, but recent research suggests that inherited mitochondrial defects may also play a role [2]. Individuals with T2D have many adverse health outcomes that make early diagnosis and treatment critical.

In recent years, high-risk groups for T2D have been targeted to determine if physiological changes occur before the onset of disease. A recent study found that women in their mid-30s with a family history (FH) of T2D have a reduced whole-body metabolism [3]. This reduction in whole-body metabolism may lead to increased fat deposition, thereby leading to insulin resistance [2]. Other work has found that individuals with an FH of T2D also have impaired vascular function years before the development of the disease [4,5]. Brachial artery flow-mediated dilation (FMD) was impaired in middle-aged normoglycemic subjects with an FH of T2D compared with healthy control subjects [4,5]. Interestingly, subjects who had an FH of T2D had a similar reduction in vascular function as individuals who were glucose intolerant [4]. These studies demonstrate that abnormalities in metabolic rate and vascular function may be present in some subjects at risk for T2D before the development of insulin resistance and T2D. The research is limited because it has not measured both metabolic and vascular function in a young, healthy, FH for T2D population and has not taken into account physical activity, which affects metabolic and vascular function.

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The purpose of this study was 2-fold: (1) to determine if young (mid-20s), insulin-sensitive, sedentary individuals with an FH of T2D (FH+) have a reduced whole-body metabolic rate (resting energy expenditure [REE]) and abnormal vascular function compared with individuals who have no FH of T2D (FH−) and (2) to determine if differences in metabolic or vascular function existed between sex. Vascular endothelial function was measured via FMD, and the blood-borne markers C-reactive protein (CRP) and interleukin-6 (IL-6) were measured as markers for vascular inflammation.

The determination of whole-body metabolism is a method that is more cost effective and readily available than investigating mitochondrial function and may be useful in determining if metabolic abnormalities exist before the development of T2D. Furthermore, vascular endothelial function as measured by an FMD is a simple noninvasive mechanism that is correlated to coronary artery endothelial function [6] and cardiovascular disease risk and mortality [7]. These methods could potentially serve as screening tools for high-risk individuals for disease.

To address these aims of the study, young (mid-20s), sedentary, men and women who had no signs of disease and had normal fasting glucose and insulin levels were recruited for the study. Individuals were classified based on FH of T2D. We hypothesized that both FH+ men and women would exhibit similar reductions in metabolic rate and impaired FMD compared with the FH− group.

2. Research design and methods

2.1. Study subjects

Forty-two subjects (20-34 years old) were recruited from a local university population (staff, faculty, and students) for participation in this study. Twenty-one individuals (11 men, 10 women) were classified as having a positive FH of T2D (*FH+*), defined as having at least one parent diagnosed with T2D after the age of 35 years, as determined through self-report. Twenty-one subjects (11 men, 10 women) reported having no parents, grandparents, or siblings diagnosed with T2D and were classified as *FH−*. Self-reported medical history and exercise data were obtained from all subjects.

Subjects were excluded if they reported having any history of disease (ie, diabetes, hypertension, hyperlipidemia, asthma) or any health problems to avoid any confounders on vascular function. No subject was taking any vasoactive medications, and smokers were not included to avoid any effects on vascular function. Individuals were excluded if they reported exercising more than 20 min/d and more than 2 d/wk over the past 6 months to control for activity effects on mitochondrial function. Ten of the 42 subjects reported some form of exercise (eg, intramural flag football, kayaking, walking, or bicycle to work) on average once a week for 20 to 30 minutes. All women were tested during the early follicular phase of their menstrual cycle to avoid any confounders of menstrual cycle on measurements. Before participation, all subjects provided written informed consent. All measurements were conducted at the Metabolic and Vascular Laboratory at the University of Louisville with approval of the Institutional Review Board.

2.2. Study design

All subjects reported to the laboratory after abstaining from food, caffeine, and alcohol for at least 12 hours, and any form of exercise for at least 24 hours. Height and weight were measured for each subject when they reported to the laboratory. Body composition was determined in the morning using bioelectrical impedance (RJL Systems, Clinton Township, MI). Total body resistance and reactance were used to calculate fat mass (FM) via computer software (Cyprus 2.7, Body Composition Analysis, RJL Systems). Fat-free mass (FFM) was calculated using a validated multiple regression equation: FFM = −8.98751 + 0.36273 (height^2 [centimeters]/resistance) + 0.21411 (height) + 0.13290 (weight [kilograms]) − 5.61911 (G), where G refers to gender and is equal to 0 if it is a male and 1 if it is a female. Resting energy expenditure was then measured followed by the vascular measurements. Lastly, a blood sample was taken from each subject to get fasting insulin and glucose concentrations.

2.3. Resting energy expenditure

Resting energy expenditure was measured first thing in the morning approximately 30 minutes after the subject's reported normal waking hour. Subjects were instructed to lie supine in a temperature-controlled (22°C-24°C) darkened room for approximately 15 minutes to habituate to the room. Measurements were taken continuously for 30 minutes, and were averaged over 1-minute intervals, by open-circuit indirect calorimetry using a transparent canopy system in the dilution testing mode (True One 2400; Parvo Medics, Sandy, UT). The REE was calculated using an abbreviated Weir equation (without urinary nitrogen): REE (kilocalories per day) = (3.9 VO_2 + 1.1 VCO_2) ∗ 1.44. The REE was expressed in 3 separate ways: kilocalories per 24 hours, kilocalories per day per kilogram of body weight to control for difference in overall BW, and kilocalories per day per kilogram of FFM to control for muscle mass.

2.4. Vascular function studies

Flow-mediated dilation was used to determine endothelial-dependent function in the subject's brachial artery using quantitative Doppler ultrasound (HDI 5000; Philips, Seattle, WA). Measurements were performed by a single investigator to avoid investigator variability. Blood pressure was measured throughout the entire testing period. The right brachial artery was imaged longitudinally, 2 cm above the antecubital fossa by B-mode ultrasound, using a 12-5–MHz linear array transducer. Reactive hyperemia was induced by inflation of a pneumatic cuff (10 cm wide) at 60 to 80 mm Hg suprasystolic for 5 minutes of the upper arm using a rapid

cuff inflator (E20; Hokanson, Bellevue, WA). Five minutes of data collection occurred both before and after cuff occlusion to determine blood velocity and diameter of the vessel. The maximal time average peak blood velocity was used to determine if the stimulus after cuff occlusion was the same for each individual. The FMD was determined as the maximal percentage change in brachial artery size after cuff occlusion compared with baseline diameter. A video was collected throughout the entire test and saved by video recording software to a computer for future analysis (Ulead Video Studio 7; Ulead Systems, Taipei, Taiwan). A custom-made software program using LabView version 7.1 (National Instruments, Austin, TX) measured the changes in the time average maximal velocity and brachial diameter on a beat-by-beat basis throughout the entire testing period.

2.5. Blood analyses

Approximately 10 mL of blood was drawn from the antecubital vein after the vascular and metabolic testing for determination of fasting plasma glucose and insulin concentrations. Samples were stored at −80°C until analyzed. All samples were analyzed using the same assays. Insulin was measured by an electrochemiluminescent double monoclonal immunometric assay (Roche Diagnostics, Indianapolis, IN). Glucose was measured via an enzymatic method (Ortho Clinical Diagnostics, Raritan, NJ) using glucose oxidase coupled to peroxidase. The concentration of IL-6 in the plasma samples was measured by a 2-site enzyme-linked immunosorbent assay and comparison with a recombinant human IL-6 standard. The assay was based on a human IL-6 enzyme-linked immunosorbent assay set (BD OptEIA; BD Biosciences, San Diego, CA). All samples were assayed in triplicate, and the results are expressed as the mean of the determinations. The lower sensitivity of the assay was 1.5 ± 0.1 pg/mL. The concentration of CRP was measured by a particle-enhanced immunoturbidimetric method (CRPLX) on the Cobas Integra 800 (Roche Diagnostics). The analytical sensitivity of the assay is 0.0085 mg/dL, and the upper limit of the reference range is 0.5 mg/dL.

Insulin resistance (IR) was calculated according to the homeostasis model assessment (HOMA) [8] using fasting insulin and glucose concentrations:

$$\text{HOMA IR} = \frac{\text{fasting insulin } (\mu\text{U/mL}) * \text{fasting glucose (mmol/L)}}{22.5}$$

2.6. Statistical analyses

Based on known sex differences in metabolic rate and because differences have been reported in women but not men, a primary aim of the study was to determine if differences existed between FH groups between sexes. The statistical analyses for between FH groups were split between sexes. A 1-way analysis of variance (ANOVA) was conducted on baseline measures using SPSS (Version 14.0; SPSS, Chicago, IL). Significant between-group differences were found on some of the baseline measurements in the female but not the male subjects; thus, separate 1-way analyses split by sex were conducted rather than a 2 × 2 factor ANOVA. For the male subjects, a 1-way ANOVA was used to determine differences between groups for the metabolic (REE, REE/FFM, and REE/BW) and vascular measurements (FMD and time average peak velocity). For the female subjects, a general linear model analysis controlling for baseline differences (body mass index [BMI] and FM) was used for the analysis of all metabolic and vascular data. Pearson correlations were conducted to determine if whole-body metabolism or FMD were correlated to insulin, glucose, CRP, IL-6, age, BMI, FFM, and FM. Differences were considered to be statistically significant at a P value < .05.

3. Results

The FH− and FH+ groups were similar in age, height, weight, and FFM (Table 1). Body mass index ($F_{1,41} = 5.066$, $P = .032$) and FM ($F_{1,41} = 3.909$, $P = .057$) were greater in the FH+ group compared with the FH− group. When groups were split by sex, it was determined that the women were primarily responsible for the between-group differences on BMI and FM, with no significant group differences between the men. The FH+ women trended toward a higher BMI ($F_{1,20} = 3.251$, $P = .075$) and FM ($F_{1,20} = 3.615$, $P = .065$) compared with FH− women. To control for BMI and FM, a general linear model analysis was used to determine if metabolic function and FMD were significantly different between groups in women.

There was no significant difference in fasting insulin ($F_{1,20} = 1.433$, $P = .251$), glucose ($F_{1,20} = 2.069$, $P = .172$), CRP ($F_{1,17} = 3.038$, $P = .101$), or IL-6 ($F_{1,16} = 1.527$, $P = .254$) between groups for the men (Table 1). For the women,

Table 1
Subject characteristics of FH+ and FH−

	Men		Women	
	FH+	FH−	FH+	FH−
Age (y)	28.1 ± 4.2	26.0 ± 4.2	26.1 ± 3.6	24.3 ± 3.6
Height	177 ± 9	184 ± 7	160 ± 6	166 ± 8
Weight	83.6 ± 10.0	85.0 ± 19.3	66.5 ± 11.7	61.1 ± 8.3
BMI*	26.5 ± 2.7	24.8 ± 4.3	25.9 ± 4.5	22.3 ± 3.1
FFM	63.4 ± 6.1	68.5 ± 8.0	43.8 ± 3.4	45.8 ± 3.8
FM†	20.2 ± 4.8	16.5 ± 11.8	22.7 ± 9.0	15.3 ± 5.9
CRP (mg/dL)	0.09 ± 0.08	0.04 ± 0.03	0.14 ± 0.13	0.11 ± 0.09
IL-6 (pg/dL)	5.1 ± 1.4	5.3 ± 3.1	6.2 ± 1.0	1.9 ± 0.3‡
Insulin (μU/mL)	12.0 ± 4.3	8.8 ± 5.9	8.5 ± 4.5	11.4 ± 3.2
Glucose (mmol/L)	5.5 ± 0.2	5.7 ± 0.3	5.2 ± 0.1	5.4 ± 0.2
HOMA IR	2.9 ± 1.1	2.2 ± 1.5	2.0 ± 1.0	2.8 ± 0.9
Systolic BP	129 ± 13	127 ± 8	105 ± 10	109 ± 10
Diastolic BP	74 ± 9	71 ± 7	67 ± 9	66 ± 10

Values are mean ± SD for FH+ and FH− groups. BP indicates blood pressure.
* $P < .032$ between-group difference with combined sexes.
† $P = .057$ between-group difference with combined sexes.
‡ $P = .065$ between-group difference.

Table 2
Metabolic data of FH+ and FH−

	Men		Women	
	FH+	FH−	FH+	FH−
REE (kcal/d)	1924.3 ± 99.5	1967.9 ± 109.5	1364.5 ± 56.1	1382.3 ± 52.1
REE/BW (kcal/[d kg BW])	23.0 ± 0.8	23.9 ± 0.8	23.4 ± 0.8	21.5 ± 0.7*
REE/FFM (kcal/[d kg FFM])	30.3 ± 1.3	28.7 ± 0.9	29.6 ± 1.2	32.1 ± 1.3
RQ	0.79 ± 0.02	0.78 ± 0.03	0.82 ± 0.01	0.80 ± 0.02*

Values are adjusted means ± SEM for men and adjusted means ± SEM controlling for fat and BMI for women.
* $P \leq .014$ between-group difference.

there was no difference between groups for fasting insulin ($F_{3,21} = 1.513$, $P = .271$), glucose ($F_{3,21} = 0.953$, $P = .452$), or CRP ($F_{3,17} = 1.109$, $P = .381$). However, the difference between groups approached significance for IL-6 ($F_{3,17} = 3.957$, $P = .065$). Insulin resistance was not significantly different between groups for the men ($F_{1,20} = 1.280$, $P = .277$) or the women ($F_{3,21} = 1.369$, $P = .308$). Insulin resistance, calculated via HOMA, indicated that all subjects were insulin sensitive [9,10]. The CRP levels were <0.21 mg/dL in all subjects, which is consistent with the fact that our subjects were insulin sensitive [11].

Metabolic data can be found in Table 2. Because of the differences in body size between individuals and the strong relation of REE to body size and FFM [12], REE was normalized to both BW (REE/BW) and FFM (REE/FFM). There were no significant differences in any of the metabolic measures for the men between FH groups. The REE normalized to BW (REE/BW) when adjusted for BMI and FM was significantly reduced in the FH+ women compared with the FH− group ($F_{3,21} = 7.930$, $P < .001$) (Fig. 1). There was no difference in REE or REE/FFM between groups for the women. Resting respiratory quotient (RQ) was significantly higher in the FH+ women than the FH− women ($F_{3,21} = 5.881$, $P = .014$) but was not different in the men ($P = .676$).

Diameter size was measured via a specialized program on a heart beat-by-beat basis. Baseline brachial artery diameter was not significantly different between groups for men (0.45 ± 0.04 vs 0.44 ± 0.05 cm, $P = .420$, FH− vs FH+, respectively) or women (0.36 ± 0.03 vs 0.35 ± 0.04 cm, $P = .561$, FH− vs FH+, respectively). Maximal diameter size occurred on average 72 ± 13 seconds in all subjects, with no differences between groups. The FMD was significantly reduced (34.3%) in FH+ women compared with FH− women ($F_{3,21} = 7.471$, $P = .002$) (Fig. 2). No significant difference in FMD was found between groups for men ($F_{1,20} = 0.824$, $P = .376$). When FMD was normalized to baseline diameter to control for diameter differences between subjects, the results were the same, with the FH+ women having a reduced response to the FH− group ($P = .003$) and no difference between the men ($P = .389$). Blood flow velocities were not different between groups either before (10.3 ± 5.9 and 11.7 ± 9.8 for FH− and FH+, respectively) or after (98.4 ± 24.0 and 101.1 ± 42.1 for FH− and FH+, respectively) cuff occlusion verifying a similar stimulus

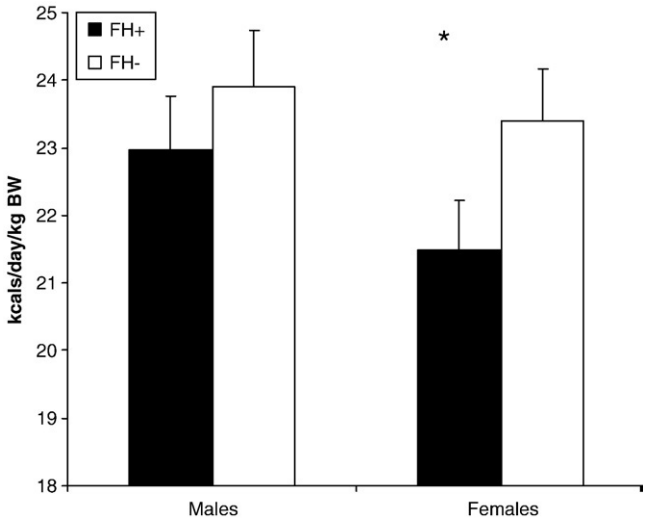

Fig. 1. Adjusted REE per kilogram BW in men and women (mean ± SEM) controlling for BMI and FM according to the presence (FH+) or absence (FH−) of an FH for T2D. *$P < .001$ between-group difference.

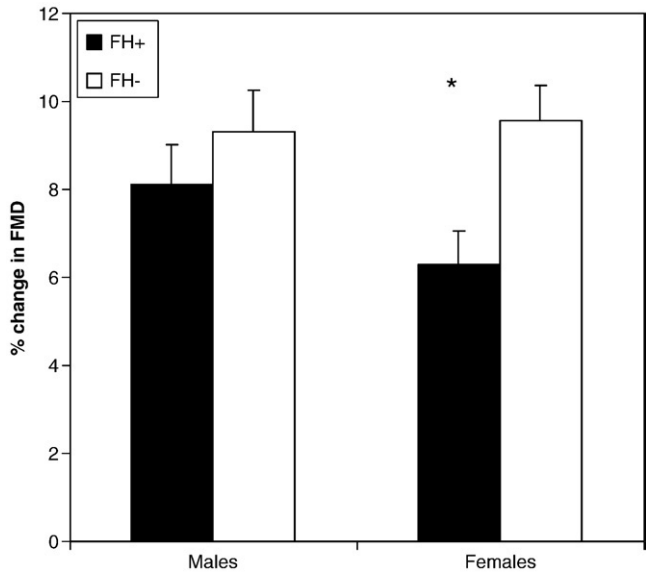

Fig. 2. Flow-mediated dilation in men (mean ± SE) and women (adjusted mean ± SE; controlling for BMI and FM) according to the presence (FH+) or absence (FH−) of an FH for T2D. *$P = .002$ between-group difference.

(shear stress) for FMD. Time average peak velocity was not significantly different between groups at baseline ($P = .376$ and $P = .524$, for men and women, respectively) or after cuff occlusion ($P = .804$ and $P = .747$, for men and women, respectively). Lastly, there was no change in blood pressure throughout the testing period for any of the subjects.

Correlation analyses were conducted to determine if FMD or metabolism was significantly correlated to IL-6, CRP, glucose, insulin, BMI, FFM, or FM. In the female subjects, FMD was not correlated to either IL-6 ($P = .151$) or CRP ($P = .210$). However, REE was significantly negatively correlated to both IL-6 ($r = -0.548$, $P = .032$) and CRP ($r = -0.531$, $P = .038$). The REE/BW was significantly negatively correlated to IL-6 ($r = -0.532$, $P = .037$) but not CRP ($r = -0.403$, $P = .097$). Lastly, IL-6 was positively correlated to glucose ($r = 0.524$, $P = .044$) in the women. The FMD was negatively correlated ($r = -0.426$, $P = .039$) to CRP in the male subjects but not for any other blood marker. No other relationships were significant for the male subjects.

4. Discussion

The primary findings of this study are that whole-body metabolism (REE/BW) and endothelium-dependent vascular function (FMD) are reduced in young, nonobese, insulin-sensitive women with an FH of T2D compared with sex- and age-matched controls with no FH. Furthermore, no differences in metabolic or vascular function were found between FH groups in male subjects. To our knowledge, this is one of the youngest (mid-20s) FH+ populations in which whole-body metabolism and vascular function have both been studied. These findings suggest that metabolic and vascular impairments occur in young, nonobese, insulin-sensitive women with an FH for T2D, suggesting that they may be at increased risk of developing T2D.

4.1. Whole-body metabolism outcomes

Our finding of a reduced whole-body metabolism in young (20s) women but not men with an FH of T2D is unique. Previous research conducted primarily on women has documented reduced REE and an increased reliance on carbohydrate use and a decreased lipid oxidation in FH+ individuals [3]; however, very little research has also looked at men. A limitation to previous work is that physical activity levels have not been reported or controlled adequately, making the findings difficult to interpret. It is well established that aerobic exercise increases mitochondrial function and whole-body metabolism by increasing mitochondrial number and mitochondrial volume [13], whereas resistance exercise also increases whole-body metabolism by its effect on muscle hypertrophy [14]. We can exclude the potential for physical activity differences explaining our findings because we controlled well for physical activity.

The mechanism for the development of T2D has not been clearly elucidated. A proposed hypothesis is that individuals who have a reduced metabolic rate may be more likely to develop T2D because of a reduction in mitochondrial activity, causing an increased storage of intramyocellular lipids within skeletal muscle. The increase in intramyocellular lipids triggers a serine kinase cascade that leads to defects in insulin signaling and reduced insulin-stimulated glucose transport [2,15]. If this proposed mechanism is correct, the reduction of whole-body metabolism in FH+ women is significant because it suggests that low metabolic rate found in 20-year–old women may serve as an important contributing factor to the pathogenesis of T2D.

Our finding of an elevated RQ in the FH+ women suggests that this group may be relying more on carbohydrate use than lipid use; however, these findings need to be confirmed because we did not control dietary intake. Increased carbohydrate use and reduced lipid oxidation have been correlated with the degree of insulin resistance in FH+ individuals [16].

Resting energy expenditure is primarily determined by age, sex, FFM, and body size [12]. The REE is often expressed only in terms of FFM; however, research in lean and obese individuals found that expressing REE in terms of FFM alone introduces error because adipose tissue is an energy-requiring tissue [17]. Fat mass contributes significantly to REE [18,19] and may be the primary determinant in influencing resting metabolic rate in women [20]. Thus, the normalization of REE by BW may be more accurate than REE normalized to FFM [17].

4.2. Vascular function outcomes

Endothelium-dependent vascular function as measured by FMD was significantly reduced in the FH+ women compared with the FH− group. Interestingly, familial history did not have adverse effects on FMD in healthy, insulin-sensitive male subjects. A reduction in FMD has been positively correlated to increased risk for cardiovascular disease [7]. Peripheral endothelial function, as measured by FMD in the brachial artery, has been closely correlated to coronary artery endothelial function [6]. Endothelial dysfunction is impaired by known coronary risk factors, including hypertension, diabetes, dyslipidemia, and FH of coronary disease [21]. The early occurrence of reduced vascular function as measured by FMD in our FH+ female population highlights the importance of identifying individuals with high disease risk early to target them for lifestyle modifications.

Our finding of reduced brachial artery FMD in young women but not men is unique. Work by Caballero et al [4] supports our findings that vascular impairments (FMD reduced by 23%) may exist in those with an FH of T2D, but their study was conducted in a much older population (average age = 49 years) and was found in both men and women [4,22]. Other works measuring vascular function via other methods have found that individuals with an FH of T2D have greater artery stiffness (carotid-radial pulse

wave velocity) [23] and less aortic distensibility compared with age- and sex-matched controls [24]. Our results in combination with previous work suggest that vascular impairments occur earlier in women than in men and that FH of T2D may play an important aspect of overall vascular health.

We did not find any significant differences between groups in blood-borne markers of vascular inflammation for the men or women. Our values of CRP were consistent with other literature, indicating that our subjects were healthy, insulin-sensitive individuals [11]. Neither CRP nor IL-6 was significantly correlated to FMD in the women; however, they were significantly negatively correlated to whole-body metabolism. Our results suggest that FMD, a nitric oxide–dependent pathway, and whole-body metabolism may be earlier markers of disease than the blood-borne markers and thus are evident in individuals who are in their 20s. Other literature has shown that CRP and IL-6 are increased in those with an FH of T2D, but these studies have used an older population than ours [25].

4.3. Sex differences

Our findings demonstrated that women with an FH of T2D have a reduced metabolic rate and vascular dysfunction that did not exist in their male counterparts. A possible explanation for the sex difference in our results may be due to differences in lipid metabolism and storage between men and women [26]. Another possible explanation could be that women have a higher resting intramyocellular fat concentration than men, which may predispose them to T2D [27], whereas still other research has shown that the development of T2D may be due to the concentration of sex-specific hormones (specifically testosterone and sex hormone binding globulin) [28]. Lastly, other research has shown that young girls (5 years) are more insulin resistant than young boys despite controlling for anthropometric and physical activity differences [29]. These factors in combination may suggest that women may be more prone to develop T2D than men [28,29].

In conclusion, this study found that REE normalized to BW and endothelium-dependent vascular function (FMD) were significantly reduced in young, sedentary, insulin-sensitive women but not men with an FH of T2D compared with those with no FH. These metabolic and vascular abnormalities occurred in apparently healthy, insulin-sensitive women who were in their mid-20s. Future work is warranted to address the sex differences in the relationship of whole-body metabolism and vascular function in those with an FH of T2D.

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