CLINICAL SCIENCES

Metabolic Dysfunction in Diabetic Offspring: Deviations in Metabolic Flexibility

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ABSTRACT

RUSSELL, R. D., R. R. KRAEMER, and A. G. NELSON. Metabolic Dysfunction in Diabetic Offspring: Deviations in Metabolic Flexibility. *Med. Sci. Sports Exerc.*, Vol. 45, No. 1, pp. 8–15, 2013. In type 2 diabetes (T2D), insulin resistance is related to comorbidities, including high lipotoxicity, poor glucoregulation, and loss of metabolic flexibility. Controversy exists regarding whether reduced metabolic flexibility precedes insulin resistance or vice versa. **Purpose**: The purpose of this study was to determine whether a family history of T2D leads to metabolic inflexibility. **Methods**: To examine potential loss of metabolic flexibility at early stages, we used a hooded metabolic cart to compare metabolic characteristics in people with T2D, family history of T2D (FH+), and controls (FH−) 1) at rest, 2) with passive stretching (PS) and recovery, and 3) with oral glucose load. Testing of 9 T2D, 11 FH+, and 9 FH− occurred after a 12-h fast under resting conditions. Expired gas and blood glucose (BG) were measured before and after each condition. **Results**: PS lowered BG ($P < 0.05$) in FH− and FH+ (mean ± SD, −2.7 ± 5.9 and −5.8 ± 7.5 $mg \cdot mL^{-1}$) compared with T2D (−0.9 ± 7.7). CHO use ($kcal \cdot min^{-1}$) increased with PS in all groups (0.04 ± 0.18, 0.03 ± 0.26, and 0.22 ± 1.6 $mg \cdot mL^{-1}$ in FH−, FH+, and T2D, respectively). For oral glucose load, different metabolic flexibility existed between FH− as well as FH+ (0.16 ± 0.07) as well as T2D (0.16 ± 0.07), with no difference between FH− and T2D. **Conclusion**: PS increases glycolytic activity without affecting BG in T2D, and reductions in metabolic flexibility exist in T2D and FH+ without glucoregulatory impairment in FH+, indicating early stage of mitochondrial dysfunction in FH+. Findings indicate PS is an important tool for assessing metabolic flexibility. **Key Words:** METABOLIC FLEXIBILITY, DIABETES, METABOLISM, DIABETIC OFFSPRING, PASSIVE STRETCHING

Type 2 diabetes (T2D) is a pandemic disease (30) characterized by insulin resistance (IR), which develops one to two decades before the onset of T2D, and is the best predictor for future development of T2D (23,24). Because IR is related to comorbidities including elevated lipid levels (8), loss of metabolic flexibility (10), and impaired glucoregulation (37), much attention has been given to studying these comorbidities.

IR subjects display impaired glucoregulatory function and impaired metabolic flexibility. Metabolic flexibility is characterized by impaired ability to switch from fat to carbohydrate as substrate from the fasted-to-fed transition (21). Factors likely to contribute to IR include decreased hexokinase activity and peroxisome proliferator-activated receptor gamma coactivator 1 expression (31). In addition, disturbances of nonesterified fatty acid (NEFA) metabolism, perturbed basal lipolytic rate, and impaired suppression of plasma NEFA concentration by insulin are also associated with IR and reduced metabolic flexibility (28). With comorbidities and additional confounding factors (e.g., obesity and impaired glucoregulatory function) often present in T2D patients, it is difficult to distinguish which factor may be the initial trigger for developing IR.

Interestingly, IR individuals with a positive family history of diabetes (FH+) are an ideal group in which to study the initial development of diabetes and its earliest comorbidities for several reasons. FH+ has been shown to have 40% higher risk for developing T2D than those with no family history (FH−) (32,38) and has impaired hexokinase II activity and PGC1 expression similar to T2D (31,33), which leads to decreased expression of nuclear respiratory factor 1 (31). The benefit of studying IR in FH+ is that these individuals often have not yet developed many of the confounding factors contributing to the development of T2D, like glucotoxicity or obesity, yet they display a 50% reduction in the rate of insulin-stimulated whole-body glucose metabolism (32), suggesting the pathogenesis of T2D in the FH+ population

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can be examined at its earliest time points (27). To date, research has been limited to sedentary, IR FH+ only, making it difficult to isolate the pathologic connection shared between FH+ and T2D, leading to the development of IR and diabetes (35,36). However, studies show that exercise training of FH+ increases metabolic functionality (MF) and glucoregulatory function to similar levels of sedentary FH− (1), which may be due to impaired insulin sensitivity and/or metabolic function before training (5). Furthermore, assessment of MF at rest may be insufficient to detect deficiencies in fat metabolism, because demand for fat oxidation at rest is minimal (16).

Therefore, the purpose of the current study was to determine whether reduced MF exists in a young, active FH+ population with normal glucoregulatory function using both traditional glucose loading and a separate stretching metabolic stimulus, and to compare the MF of physically active FH− with that of physically active FH+ and T2D patients. *In vivo* physiological data presented from the present study could potentially aid in development of effective screening tools and interventions to prevent T2D progression in the FH+ population.

Because FH+ and T2D populations display impaired hexokinase and peroxisome proliferator-activated receptor gamma coactivator 1 (31,33), it was hypothesized that that FH− would be more metabolically flexible than FH+ and T2D as measured by changes in RER after an oral glucose load (OGL). Furthermore, we hypothesized that passive stretching (PS), a form of mild physical activity, would elicit a more substantial shift in substrate use in FH− compared with FH+ and T2D because of the greater metabolic demands of mild exercise (16) than that of a traditional MF test using glucose loading.

METHODS

Subjects. Thirty-seven subjects were recruited from the Baton Rouge area using word of mouth to participate in one morning of fasting metabolic testing. FH+ was categorized as a first- or second-degree relative of a person with T2D. Previous studies have classified FH+ as only a first-degree relative; however, recent epigenetic investigations suggest that heritable traits may be passed as far as three generations (13). The subject population consisted of 10 healthy active controls with no family history (FH−) of diabetes, 16 FH+, and 11 T2D subjects. Age, sex, body mass index (BMI), and physical activity level were matched between FH+ and FH−. The purpose, potential risks, and benefits of participation in the study were explained to each participant before written consent was obtained before testing. The study was approved by the Louisiana State University Institutional Review Board. All FH+ and FH− subjects had normal fasting blood glucose (BG) before testing as determined by a finger prick and glucometer (Accu-Chek Compact Plus, Indianapolis, IN). Additional inclusion criteria for FH+ and FH− groups were no overt disease, including but not limited to cardiovascular disease, hypertension, impaired glucose tolerance kidney, or renal disease, BG concentrations under 10 $mmol \cdot L^{-1}$ (180 $mg \cdot dL^{-1}$) 1 h after glucose loading, BMI between 18.5 and 24.9 $kg \cdot m^{-2}$, physically active, and not taking prescription medication other than oral contraceptives. T2D subjects had no diseases other than T2D (i.e., no comorbidities), nor were any of the subjects taking prescription drugs other than prescribed glucose-regulating medications (i.e., none were taking insulin). Mean BMI ± SE for the T2D group was 27.6 ± 1.3, which indicates these subjects were overweight. A medical history and physical activity questionnaire were completed before participation in the study to determine eligibility. Subject characteristics are summarized in Table 1.

Research design. The study used the standardized method using indirect calorimetry to assess metabolic flexibility (26) under traditional insulin stimulation via an OGL and a novel, low-intensity metabolic stimulus. The study consisted of a single session with three components designed to determine metabolic flexibility: 1) assessment of fasting/resting capillary glucose concentrations and metabolic rate (RMR) including substrate oxidation via indirect calorimetry, 2) assessment of physiological responses to the low-intensity metabolic stimulus of PS, including changes in capillary glucose concentration, and 3) assessment of physiological responses to an OGL, including changes in capillary glucose concentrations and changes in substrate oxidation via indirect calorimetry. The glucose meter used in the present study has been shown to have similar precision as other glucose meters used to monitor glucose concentrations in diabetic patients (34). For each subject, we used the same glucose meter across time, which allowed us to accurately compare changes in response to glucose load and stretching. After standard calibrationc procedures, all capillary glucose measurements were determined in duplicate with no more than 3 $mg \cdot dL^{-1}$ variation between duplicate measures of the same concentration. This ensured reliability of the glucose determinations.

RMR assessment. Participants reported to the laboratory to begin the study at 7:45 a.m. after a 10-h fast. Participant's height and weight were measured; then at 8:00 a.m., they were placed in the supine position for 30 min before RMR testing. During this time, fasting BG was determined by finger prick and measured by glucometer analysis (Accu-Chek Compact Plus), a precise and reliable means of assessing BG (34). After the initial 30-min rest period, a canopy connected to a metabolic system was placed over the subject's head to collect and analyze resting expired gases for 50 min. This time included a 20-min stabilization period followed by 30 min of data collection with continual monitoring to ensure wakefulness. Figure 1 shows a timeline for the morning testing session. Expired gases were analyzed using a metabolic system (Moxus Max-II, AEI

TABLE 1. Subject characteristics: age (yr), height (cm), weight (cm), and BSA (mean ± SE).

	FH+	FH−	T2D	*P*
Age (yr)	24 ± 1.1	23.1 ± 2.0	37.7 ± 6.1*	0.01
Height (cm)	170.5 ± 2.9	173.8 ± 1.9	170.0 ± 3.3	NS
Weight (kg)	70.6 ± 3.2	76.0 ± 3.2	88.4 ± 6.8*	0.037
BSA	1.81 ± .06	1.90 ± .05	1.98 ± .08	NS

NS, not significant.
* Significantly different than FH+ and FH−.

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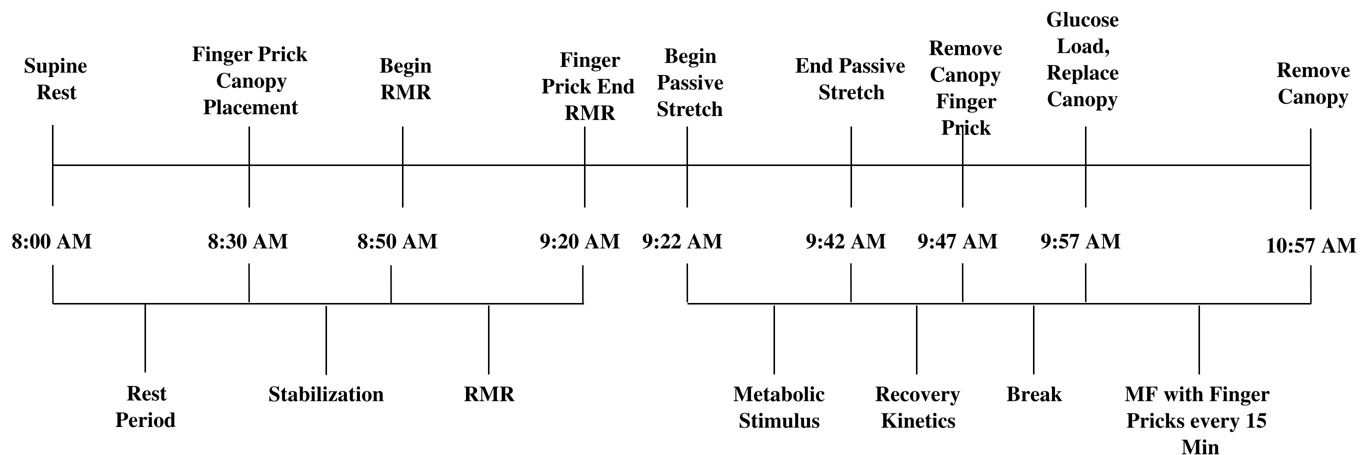

FIGURE 1—Timeline of study test morning.

Metabolic Systems, software version 2.7.01, Naperville, IL) that was calibrated using two gas mixtures with known O_2 and CO_2 composition before each test. After 20 min in which RMR data stabilized, the subsequent 30 min of RMR were recorded and used for analysis as fasting oxygen kinetics at rest (Fig. 1).

Metabolic response to passive stretch. At 9:22 a.m., immediately after RMR, another duplicate BG assessment was conducted via finger prick, and 20 min of PS was performed while the participants rested under the metabolic canopy. PS was conducted by the same laboratory technician on all participants while gases were collected under the canopy to determine specific substrate use and metabolic rate. Standardized procedure for PS included maximal pain-free stretch relative to each muscle group for each participant. Participants were instructed to lift one finger when maximal relative stretch was attained. When the appropriate tension was reached, the stretch was held for 20 s and then repeated after a 10-s break. Muscles stretched included gastrocnemius, hamstring, quadriceps, hip abductors, gluteal muscles, pectorals major and minor, and forearms, respectively, on the left and then right sides of the body. Recovery metabolic data were collected for 5 min poststretching to measure recovery oxygen consumption and substrate use, and then postrecovery determination of BG was again conducted in duplicate via finger prick and glucometer analysis. Because the metabolic stimulus from PS was considered constant for the entire 20 min, peak stretching values consisted of average values during the last 5 min of PS. Poststretching recovery values consisted of the last minute of the 5-min recovery period (Fig. 1).

Metabolic flexibility assessment—responses to glucose loading. After stretching and recovery, participants were given a 10-min rest before MF testing using an oral glucose dose rather than an insulin clamp as conducted in previous studies (20,35). The 10-min rest allowed $\dot{V}O_2$ and RER to return to verified prestimulated levels. Although still fasting, each participant consumed a 50-g glucose solution dissolved in 296 mL of water. Each glucose beverage was consumed within 2 min, then the participants returned to the supine position with the metabolic canopy over their heads for another 60 min with continual monitoring to ensure wakefulness (25). BG was analyzed via finger prick and glucometer in duplicate every 15 min for 1 h to determine BG responses to the OGL, and expired gas was continuously measured for 60 min similar to studies examining postprandial hyperglycemia (9,11).

Analyses. RMR was computed in part by Moxus software, including $\dot{V}O_2$ (mL·kg^{-1}·min^{-1}), $\dot{V}CO_2$ (mL·kg^{-1}·min^{-1}), nonprotein RER, $\dot{V}_EO_2$ (L·mL^{-1}), $\dot{V}_ECO_2$ (L·mL^{-1}), as well as $\dot{V}O_2$ and $\dot{V}CO_2$ adjusted for body surface area (BSA) (mL·m^{-2}). RMR was calculated with consideration of protein metabolism along with fat (g), fat (kcal), and CHO (kcal) using the abbreviated formulas of Weir (39). MF was calculated, in which MF = (RER stimulus) − (RER rest) (14), where RER stimulus was average RER every 30 s during the hour after glucose loading.

Subject characteristics were analyzed using one-way ANOVA. Prestretch RMR, BG concentration after glucose loading, and MF area under the curve (AUC) differences between groups were calculated using a one-way ANOVA with Tukey *post hoc* comparisons. Changes pre- to poststretching and pre– to post–BG concentrations were analyzed using repeated measures with Tukey *post hoc* comparisons to determine the magnitude of change differences between groups. Pearson product moment correlations were used to determine relationship between variables. All comparisons were considered significant at the alpha level $P = 0.05$.

RESULTS

RER is commonly used to assess substrate oxidation and metabolic flexibility in various populations (10,22,26). T2D were characterized by greater weight, BMI, and age than FH+ or FH− (Table 1) and had significantly higher fasting BG than the other groups (Table 2). No significant differences in resting metabolism were noted between any of the groups. A physical activity questionnaire revealed no significant differences between FH− and FH+ before the study for frequency of resistance (2.2 ± 0.35 vs 3.2 ± 0.90 times per week) or

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TABLE 2. Mean ± SE for relative $\dot{V}O_2$, RER, glucose, CHO, and fat used at rest for FH−, FH+, and T2D.

	Prestretching			Peak stretching			Postrecovery		
	FH−	FH+	T2D	FH−	FH+	T2D	FH−	FH+	T2D
$\dot{V}O_2$ (mL·kg^{-1}·min^{-1})	3.17 ± 0.29	2.89 ± 0.16	2.68 ± 0.32	3.56 ± 0.22	3.23 ± 0.24	3.17 ± 0.3	3.45 ± 0.23	3.24 ± 0.13	2.49 ± 0.44
Δ% $\dot{V}O_2$				12.3 ± 2.2	11.8 ± 2.4	18.3 ± 2.3			
RER	0.78 ± 0.02	0.78 ± 0.02	0.76 ± 0.02	0.78 ± 0.01	0.79 ± 0.01	0.79 ± 0.03	0.8 ± 0.01	0.82 ± 0.02	0.73 ± 0.05
Glucose (mg·dL^{-1})	85.1 ± 1.8	91.2 ± 2.9	108.9 ± 7.3[a,b]	–	–	–	82.3 ± 2.8[c]	84.2 ± 1.6[c]	102.3 ± 5.1[a,b,c]
CHO (kcal·min^{-1})	0.30 ± 0.07	0.31 ± 0.06	0.26 ± 0.07	0.33 ± 0.05[c]	0.44 ± 0.07[c]	0.59 ± 0.19[c]	0.62 ± 0.14	0.54 ± 0.06	0.30 ± 0.08[a]
Fat (kcal·min^{-1})	0.75 ± 0.08	0.72 ± 0.07	0.79 ± 0.08	0.86 ± 0.11	0.79 ± 0.09	0.75 ± 0.10	0.70 ± 0.04[c]	0.67 ± 0.06[c]	0.63 ± 0.10[c]

[a] Change significantly different than FH− at 0.05.
[b] Change significantly different than FH+ at 0.05.
[c] Significant from previous measurement at 0.05.

aerobic exercise (3.09 ± 0.98 vs 4.47 ± 1.12 times per week). Moreover, no differences were revealed for hours spent in either resistance exercise (2.8 ± .51 vs 2.2 ± 0.46 h·wk^{-1}) or aerobic exercise (5.4 ± 1.65 vs 5.1 ± 1.51 h·wk^{-1}) between the groups.

Metabolic responses to PS. Percentage change in relative $\dot{V}O_2$ increased with stretching in FH−, FH+, and T2D (Table 2) with no significant differences between groups (P = 0.83). Changes in kilocalories per minute of both fat and CHO differed between T2D and FH− from rest to peak PS (Fig. 2A) and subsequent recovery (Fig. 2B); however, there was no difference in these responses between T2D and FH+ (Fig. 2A, B). CHO use increased overall with stretching (P = 0.01) with a trend of more increased CHO use for FH− to FH+ to T2D (Fig. 2A). Moreover, a rapid return of CHO use from peak stretching to the last minute of the 5-min recovery was noted overall with greater change in T2D than FH− (P = 0.029) but no difference when T2D was compared with FH+ (P = 0.72) (Fig. 2B). The rapid return of CHO use for FH+ was not significantly different than either T2D (P = 0.11) or FH− (P = 0.39) (Fig. 2B). In addition, BG dropped from pre- to poststretching overall (P = 0.03) with greater BG decline in T2D than both other groups (P = 0.001). Increases in overall fat use with stretching were nonsignificant (P = 0.29). Changes in RER with stretching or recovery were not significantly different between groups (P = 0.16). Specific differences between groups in prestretching, peak stretching, and postrecovery values are shown in Table 2. Although there is a trend for FH+ to display increased CHO use from prestretching to peak PS, we were not able to detect a significant difference between FH+ and FH−. However, the findings that there were no significant differences in CHO use between not only FH+ and FH− but also between FH+ and T2D suggest that CHO use in FH+ subjects is somewhere in between the healthy state of FH− and the disease state displayed by T2D. Although no clinical significance for FH+ was revealed, these data appear to have potential diagnostic value to test for altered metabolism in FH+ individuals with normal glucose tolerance.

Metabolic responses to glucose loading. BG concentrations were significantly higher for T2D than FH+ and FH− at all time points and 30% higher at 1 h after glucose loading. Resting energy expenditure and relative $\dot{V}O_2$ remained constant throughout the 1 h after glucose loading period (P = 0.73 and 0.82, respectively) with no differences between the groups (P = 0.52 and 0.71, respectively). Also, MF AUC BG concentrations were higher for FH− than either FH+ or T2D, with no differences between FH+ and T2D (Fig. 3).

DISCUSSION

This is the first study to demonstrate that physically active FH+ subjects exhibit similar metabolic inflexibility in response to a glucose load as T2D in contrast to physically active FH− subjects, and that PS stimulates CHO use more in T2D and FH+ than FH−. No baseline differences in RMR, $\dot{V}O_2$, resting energy expenditure, fat, or CHO use were noted between T2D, FH+, or FH−. As expected, fasting BG was higher in T2D than other groups with no difference in CHO oxidation. Contrary to a previous study (10), fasting whole-body fat oxidation was no different at rest in T2D than FH− in

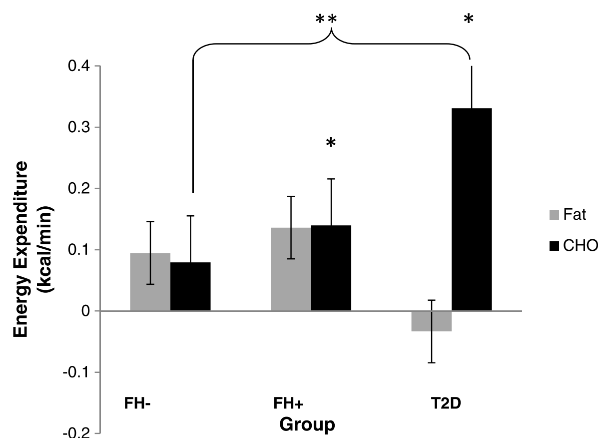

FIGURE 2—A, Change in substrate use from rest to peak PS showing significant increase in CHO use in overall group, with more significant changes in T2D than FH− or FH+ (*P* = 0.001). Mean ± SE, *n* = 10, 16, and 11 in FH−, FH+, and T2D, respectively. B, Changes in fat and CHO kilocalories per minute from peak stretching to recovery. Significant drop in fat use from peak stretch to recovery, and significantly less CHO use in T2D than FH−. *Significant change from pre to post (*P* = 0.01). **Change significantly between groups (*P* = 0.001) (mean ± SE).

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the present study. In support of the secondary hypothesis, in response to PS, FH+ displayed impaired substrate shifts between that of FH− and T2D as noted by the lack of significant differences between FH+ and either of the other two groups. PS caused increased metabolism overall; however, the T2D group displayed greater increase in CHO use during PS than FH−, which quickly returned to prestretched levels during recovery. Lastly, 60-min BG concentrations AUC for T2D were higher than FH+ or FH−.

Stretching. PS increased $\dot{V}O_2$ and RER, which is consistent with previous data indicating stretching increases metabolism and CHO use (40). Studies have shown that *in vitro*, muscle passively stretched exhibits increased heat production and oxygen consumption (3,40) similar to our indirect calorimetry findings. Similarly, PS increases glycogen breakdown (4) and lactic acid production (3) and decreases phosphocreatine concentrations (2), indicating that PS stimulates phosphagen and carbohydrate metabolism.

Because increased metabolic activity is related to increased activation of the 5' adenosine monophosphate-activated protein kinase GLUT 4 activation pathway (12,29,41), it is plausible that the increased metabolic activity accompanying passive muscle stretching activates GLUT 4 in the stretched muscles (18), explaining the increased CHO use observed with stretching in the present study (Fig. 2).

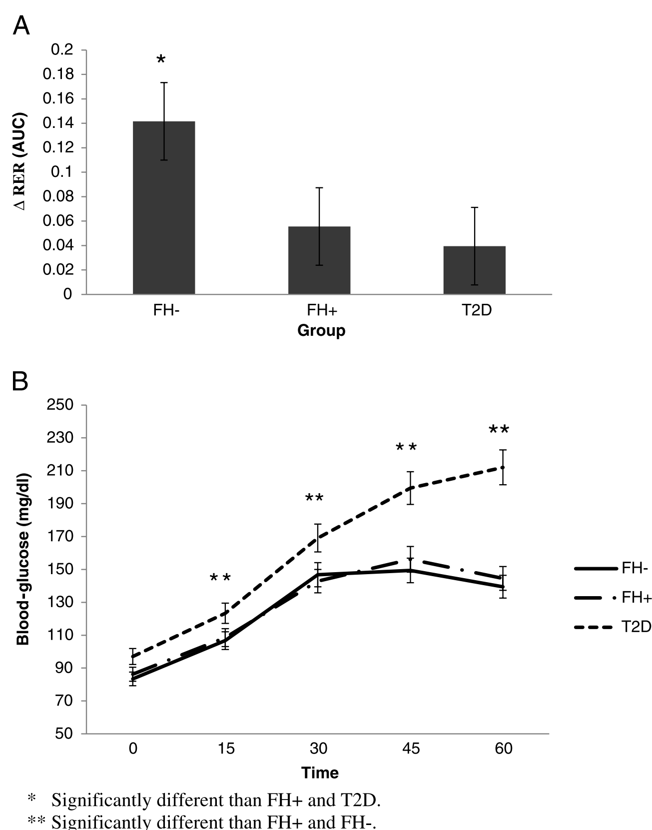

FIGURE 3—A, One-hour BG concentrations after glucose loading indicate significantly worse glucoregulatory function in T2D than FH+ or FH− (P = 0.002). B, Mean ± SE for metabolic flexibility: (RER during glucose load) − (RER fasting) AUC. *Significantly different than FH− (P = 0.002).

In previous studies, similar substrate use was observed between T2D and controls while T2D displayed significantly greater NEFA turnover (6). Similar to previous exercise and recovery findings in T2D (7,19), BG declined significantly after PS during the recovery period; however, the reductions were greater in T2D than FH− or FH+ (P = 0.001), likely because of the higher starting point for T2D. However, FH− and FH+ had similar reductions in BG concentrations as a result of PS. Although the previous studies differ from ours in that there was prior exercise to stretching and recovery, the results of the current study indicate that PS affects glucose concentrations similarly to mild exercise. Interestingly, unlike previous studies, the metabolic stimulus used in the present study (PS) stimulated metabolism to a much smaller degree, indicating magnitude of energy expenditure may be less important than a mechanical stimulus (stretching) to reduce plasma glucose. This is in accordance with previous findings (17). Although BG remained stable from the time before RMR testing though the minutes were preceding passive stretch, BG significantly decreased in all groups. However, BG significantly declined with PS to a greater extent in T2D than that in FH+ and FH− (−2.8, −6.0, and −6.6 in FH−, FH+, T2D, respectively). There was no significant difference between groups regarding absolute change from prestretching to postrecovery (P = 0.75). That BG was lower across all groups with stretching supporting the concept that PS activates non–insulin-induced GLUT4 translocation (18). Although our methods did not specifically isolate glycogen turnover, the increased CHO use occurred simultaneously with reduction in BG, further supporting the previous contention that glycogen turnover is affected by glucose transport (27). However, it was not possible within the constraints of this study to determine a timeline for reduced BG versus increased CHO use with stretching and thus also not possible to establish which precedes the other. However, in the current study, there was a significant correlation between decreased BG and increased CHO use from pre- to poststretching overall (r = 0.385, P = 0.027), demonstrating a direct relationship between the two.

CHO use from peak stretch to recovery revealed a greater reduction in the T2D group than FH−, similar to a previous mouse model study (7), but there was no significant difference between FH+ and either FH− or T2D. These findings indicate the following: 1) although stretching causes increased CHO use and decreased BG concentration, greater CHO use from PS is short lived during recovery for T2D subjects, and 2) FH+ subject responses were between those of FH− and T2D for increased CHO use and decreased BG changes. The latter indicates that although FH+ subjects displayed no overt signs of IR, they may be an ideal group to investigate the earliest phases of pathologic development of metabolic complications leading to IR.

Although greater reduction of BG was noted in the T2D group than that in FH−, the T2D had a significantly higher fasting BG, which would indicate that greater reductions are more likely. However, a larger drop in CHO use

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poststretching in T2D than that in FH− or FH+ was noted, indicating that without a metabolic stimulus, T2D subjects are not as effective at using CHO during passive recovery. These data suggest that stretching may be able to increase MF somewhat in adversely affected populations; however, because the metabolic stimulus was so low, it is likely that a more intense stimulation may increase postexercise metabolic demands and thus prolong the beneficial effects of increased metabolism.

Metabolic flexibility. Though IR was not assessed, OGTT revealed FH− and FH+ groups had similar BG responses that were better than the T2D group, in agreement with previous findings (16). Given the age, BMI, activity level, and OGTT of the FH+ group, it is unlikely that they experienced IR.

It was expected that the T2D group would display impaired glucoregulatory function and metabolic flexibility compared with FH−, given the differences in age, weight, and diabetes status. In the current study, a family history of T2D was categorized by first- and second-degree offspring of people with T2D. This categorization is supported by a recent epigenetic study indicating that heritable traits are passed on at least two generations (13). In addition, not only this group was age, BMI, and activity matched with the FH− group but also, unlike previous studies (35), both groups were highly physically active as determined by an exercise questionnaire. Thus, metabolic inflexibility in this group is a novel finding (Figs. 3B and 4) given the level of intensity and duration of physical activity. Moreover, although the T2D group displayed lower RER at 60 min after glucose loading than other groups, FH− was more metabolically flexible as per AUC and acutely at 15, 30, 45, and 60 min after glucose loading than FH+ and T2D. The degree of MF impairment in FH+ was not only worse than FH− but actually matched that of the T2D group. This suggests that independent of favorable OGTT results or fasting BG levels, FH+ and T2D are less able to effectively shift substrate use after ingesting glucose than FH−.

Previous studies indicate reduced MF is likely due to declining glucose disposal rate (15) or high fasting BG concentrations (16), although in the current study, stretching induced reduced BG concentration, and both FH− and FH+ had similar fasting BG concentration. This would suggest that other factors may affect MF, including leptin, which has been shown to affect insulin sensitivity index (5).

The T2D group displayed greater decreases in fat oxidation with glucose stimulus than FH−, although FH+ showed no differences between either FH− or T2D. This indicates that T2D are less able to shift from fat oxidation than FH−, and that FH+ have metabolic function in between FH− and T2D. This decreased fat oxidation with glucose stimulus could be due to competitive inhibition that fat oxidation elicits on glycolysis (10,16,33), the supply of fat outpacing energy needs leading to partial breakdown of fat (10,28), or a build-up of lipid intermediates such as diacylglycerol, or c-Jun N-terminal kinase (11).

Although this study did not use insulin and glucose clamps, tracers, or magnetic resonance spectroscopy, it does illustrate that MF can be measured in as little as 1 h using indirect calorimetry. The method for BG analysis is a precise and reliable means of assessing BG (34), especially with the practice of duplicate testing used in the present study. Although there was no control diet given in the present study, participants were in a 10-h fast upon arrival and an 11-h fasted state before the glucose load and MF assessment, which began over an hour after arrival. It has also been reported that regulation of respiratory quotient (RQ)/RER is an important reason for administering a control diet for MF testing (16). In order for food quotient to become equal to RQ, it could take up to one wk of regulated diet (16). Because some studies report higher fasting RQ/RER in T2D than controls, calculations of reduced MF are skewed by a higher starting RQ (16). However, in this study, there were no differences in fasting RER between groups, making it less critical to control diet. Lastly, the T2D group was older than either the FH− or FH+ groups. However, the purpose for including a T2D group was to establish a point of reference for advanced diabetes. As such, FH+ displaying similar metabolic inflexibility to T2D, even with significant age differences, is further evidence that having a family history of T2D is an important factor in aberrant metabolic function.

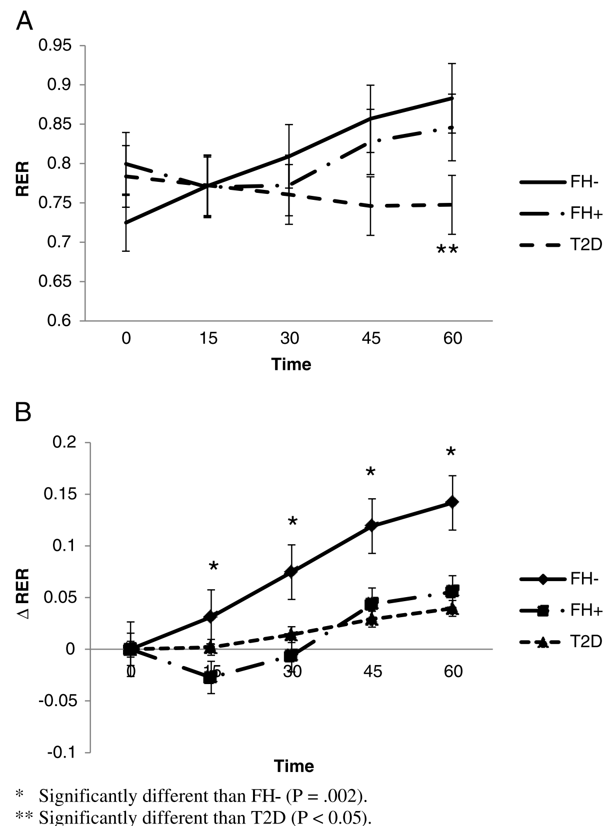

FIGURE 4—Mean ± SE for RER (A) and change in RER (metabolic flexibility) (B) up to 1 h after glucose loading.

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The current study also included three strongly defined populations. In addition, FH− and FH+ were matched for age, height, weight, and activity level, and in spite of the closely matched groups, FH+ and T2D still exhibited reduced MF relative to FH−.

CONCLUSION

This is the first study to demonstrate that physically active FH+ subjects exhibit similar metabolic inflexibility in response to a glucose load as T2D in contrast to physically active FH− subjects, and that PS stimulates CHO use more in T2D and FH+ than FH−. Therefore, FH+ either with no IR or low-level IR may be an ideal group to study mechanisms that could potentially lead to the development of IR. Future work is needed to investigate lipid intermediate kinetics of fat oxidation in FH+, such as diacylglycerol and NEFA, and to determine the dose response to stretching and exercise.

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The results of the present study do not constitute endorsement by the American College of Sports Medicine.

REFERENCES

1. Ahn CW, Song YD, Nam JH, et al. Insulin sensitivity in physically fit and unfit children of parents with type 2 diabetes. *Diabet Med*. 2004;21(1):59–63.
2. Aubert X, Marechal G. The energy balance of muscular contractions with positive or negative work. *J Physiol (Paris)*. 1963;55:186–7.
3. Barnes WS. Respiration and lactate production in isolated frog skeletal muscle: effects of passive stretch. *Comp Biochem Physiol A Comp Physiol*. 1987;86(2):229–32.
4. Barnes WS, Worrell GA. Glycogen utilization in isolated frog muscle: an effect of passive mechanical stretch. *Comp Biochem Physiol A Comp Physiol*. 1985;81(2):243–6.
5. Barwell ND, Malkova D, Moran CN, et al. Exercise training has greater effects on insulin sensitivity in daughters of patients with type 2 diabetes than in women with no family history of diabetes. *Diabetologia*. 2008;51(10):1912–9.
6. Blaak EE, van Aggel-Leijssen DP, Wagenmakers AJ, et al. Impaired oxidation of plasma-derived fatty acids in type 2 diabetic subjects during moderate-intensity exercise. *Diabetes*. 2000;49 (12):2102–7.
7. Boon H, Blaak EE, Saris WH, et al. Substrate source utilisation in long-term diagnosed type 2 diabetes patients at rest, and during exercise and subsequent recovery. *Diabetologia*. 2007;50(1):103–12.
8. Carpentier AC. Postprandial fatty acid metabolism in the development of lipotoxicity and type 2 diabetes. *Diabetes Metab*. 2008; 34(2):97–107.
9. Ceriello A. Postprandial hyperglycemia and diabetes complications: is it time to treat? *Diabetes*. 2005;54(1):1–7.
10. Corpeleijn E, Saris WH, Blaak EE. Metabolic flexibility in the development of insulin resistance and type 2 diabetes: effects of lifestyle. *Obes Rev*. 2009;10(2):178–93.
11. Da Ros R, Assaloni R, Ceriello A. Postprandial hyperglycemia and diabetic complications. *Recenti Prog Med*. 2005;96(9):436–44.
12. Dohm GL. Invited review: regulation of skeletal muscle GLUT-4 expression by exercise. *J Appl Physiol*. 2002;93(2):782–7.
13. Dunn GA, Bale TL. Maternal high-fat diet effects on third-generation female body size via the paternal lineage. *Endocrinology*. 2011;152(6):2228–36.
14. Frayn KN. Calculation of substrate oxidation rates in vivo from gaseous exchange. *J Appl Physiol*. 1983;55(2):628–34.
15. Galgani JE, Heilbronn LK, Azuma K, et al. Metabolic flexibility in response to glucose is not impaired in people with type 2 diabetes after controlling for glucose disposal rate. *Diabetes*. 2008;57(4): 841–5.
16. Galgani JE, Moro C, Ravussin E. Metabolic flexibility and insulin resistance. *Am J Physiol Endocrinol Metab*. 2008;295(5):E1009–17.
17. Hansen D, Dendale P, Jonkers RA, et al. Continuous low- to moderate-intensity exercise training is as effective as moderate- to high-intensity exercise training at lowering blood HbA(1c) in obese type 2 diabetes patients. *Diabetologia*. 2009;52(9):1789–97.
18. Ito Y, Obara K, Ikeda R, et al. Passive stretching produces Akt- and MAPK-dependent augmentations of GLUT4 translocation and glucose uptake in skeletal muscles of mice. *Pflugers Arch*. 2006; 451(6):803–13.
19. Kang J, Kelley DE, Robertson RJ, et al. Substrate utilization and glucose turnover during exercise of varying intensities in individuals with NIDDM. *Med Sci Sports Exerc*. 1999;31(1):82–9.
20. Kelley DE, Simoneau JA. Impaired free fatty acid utilization by skeletal muscle in non–insulin-dependent diabetes mellitus. *J Clin Invest*. 1994;94(6):2349–56.
21. Koves TR, Ussher JR, Noland RC, et al. Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance. *Cell Metab*. 2008;7(1):45–56.
22. Lattuada G, Costantino F, Caumo A, et al. Reduced whole-body lipid oxidation is associated with insulin resistance, but not with intramyocellular lipid content in offspring of type 2 diabetic patients. *Diabetologia*. 2005;48(4):741–7.
23. Lillioja S, Mott DM, Howard BV, et al. Impaired glucose tolerance as a disorder of insulin action. Longitudinal and cross-sectional studies in Pima Indians. *N Engl J Med*. 1988;318(19):1217–25.
24. Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. *Science*. 2005;307(5708):384–7.
25. Manco M, Panunzi S, Macfarlane DP, et al. One-hour plasma glucose identifies insulin resistance and beta-cell dysfunction in individuals with normal glucose tolerance: cross-sectional data from the Relationship between Insulin Sensitivity and Cardiovascular Risk (RISC) study. *Diabetes Care*. 2010;33(9):2090–7.
26. Meex RC, Schrauwen-Hinderling VB, Moonen-Kornips E, et al. Restoration of muscle mitochondrial function and metabolic flexibility in type 2 diabetes by exercise training is paralleled by increased myocellular fat storage and improved insulin sensitivity. *Diabetes*. 2010;59(3):572–9.
27. Morino K, Petersen KF, Shulman GI. Molecular mechanisms of insulin resistance in humans and their potential links with mitochondrial dysfunction. *Diabetes*. 2006;55(Suppl 2):S9–15.
28. Muoio DM. Intramuscular triacylglycerol and insulin resistance: guilty as charged or wrongly accused? *Biochim Biophys Acta*. 2010; 1801(3):281–8.
29. Musi N, Hayashi T, Fujii N, et al. AMP-activated protein kinase activity and glucose uptake in rat skeletal muscle. *Am J Physiol Endocrinol Metab*. 2001;280(5):E677–84.
30. O'Rahilly S. Science, medicine, and the future. Non–insulin dependent diabetes mellitus: the gathering storm. *BMJ*. 1997;314 (7085):955–9.

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31. Patti ME, Butte AJ, Crunkhorn S, et al. Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: potential role of PGC1 and NRF1. *Proc Natl Acad Sci U S A*. 2003;100(14):8466–71.
32. Rothman DL, Magnusson I, Cline G, et al. Decreased muscle glucose transport/phosphorylation is an early defect in the pathogenesis of non–insulin-dependent diabetes mellitus. *Proc Natl Acad Sci U S A*. 1995;92(4):983–7.
33. Shulman GI. Cellular mechanisms of insulin resistance. *J Clin Invest*. 2000;106(2):171–6.
34. Thomas LE, Kane MP, Bakst G, et al. A glucose meter accuracy and precision comparison: the FreeStyle Flash Versus the Accu-Chek Advantage, Accu-Chek Compact Plus, Ascensia Contour, and the BD Logic. *Diabetes Technol Ther*. 2008;10(2):102–10.
35. Ukropcova B, Sereda O, de Jonge L, et al. Family history of diabetes links impaired substrate switching and reduced mitochondrial content in skeletal muscle. *Diabetes*. 2007;56(3):720–7.
36. Valdez R. Detecting undiagnosed type 2 diabetes: family history as a risk factor and screening tool. *J Diabetes Sci Technol*. 2009;3(4):722–6.
37. van Dijk JW, Manders RJ, Hartgens F, et al. Postprandial hyperglycemia is highly prevalent throughout the day in type 2 diabetes patients. *Diabetes Res Clin Pract*. 2011;93(1):31–7.
38. Warram JH, Marin BC, Krolewski AS, Soeldner JS, Kahn CR. Slow glucose removal rate and hyperinsulinemia precede the development of type ii diabetes in the offspring of diabetic parents. *Ann Intern Med*. 1990;152(12):909–15.
39. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. *J Physiol*. 1949;109(1–2):1–9.
40. Whalen WJ, Collins LC, Berry H. Effect of stretch on O_2 consumption of resting and active frog sartorius muscle. *Am J Physiol*. 1962;203:731–4.
41. Winder WW. Energy-sensing and signaling by AMP-activated protein kinase in skeletal muscle. *J Appl Physiol*. 2001;91(3):1017–28.

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