



Exercise-induced improvements in glucose effectiveness are blunted by a high glycemic diet in adults with prediabetes

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Abstract

Aims Glucose effectiveness (GE) refers to the ability of glucose to influence its own metabolism through insulin-independent mechanisms. Diminished GE is a predictor of progression to type 2 diabetes. Exercise training improves GE, however, little is known about how dietary interventions, such as manipulating the glycemic index of diets, interact with exercise-induced improvements in GE in at-risk populations.

Methods We enrolled 33 adults with obesity and pre-diabetes (17 males, 65.7 ± 4.3 years, 34.9 ± 4.2 kg m⁻²) into a 12-week exercise training program (1 h day⁻¹ and 5 day week⁻¹ at ~85% of maximum heart rate) while being randomized to concurrently receive either a low (EX-LOG: 40 ± 0.3 au) or high (EX-HIG: 80 ± 0.6 au) glycemic index diet. A 75-g oral-glucose-tolerance test (OGTT) was performed before and after the intervention and GE was calculated using the Nagasaka equation. Insulin resistance was estimated using a hyperinsulinemic-euglycemic clamp and cardiorespiratory fitness using a VO_{2max} test.

Results Both EX-LOG and EX-HIG groups had similar improvements in weight (8.6 ± 5.1 kg, $P < 0.001$), VO_{2max} (6 ± 3.5 mL kg⁻¹ min⁻¹, $P < 0.001$) and clamp-measured peripheral insulin resistance (1.7 ± 0.9 mg kg⁻¹ min⁻¹, $P < 0.001$), relative to baseline data. GE in EX-LOG and EX-HIG was similar at baseline (1.9 ± 0.38 vs. 1.85 ± 0.3 mg dL⁻¹ min⁻¹, respectively; $P > 0.05$) and increased by ~20% post-intervention in the EX-LOG arm (Δ GE: 0.07 – 0.57 mg dL⁻¹ min⁻¹, $P < 0.05$). Plasma free fatty acid (FFA) concentrations also decreased only in the EX-LOG arm (Δ FFA: 0.13 ± 0.23 mmol L⁻¹, $P < 0.05$).

Conclusions Our data suggest that a high glycemic index diet may suppress exercise-induced enhancement of GE, and this may be mediated through plasma FFAs.

Keywords Aerobic exercise training · Glycemic index · Diet · Glucose effectiveness · Hyperinsulinemic-euglycemic clamp · Prediabetes

Abbreviations

GE Glucose effectiveness
oGE Oral surrogate of glucose effectiveness

GI Glycemic index
EX-LOG Exercise + low glycemic index diet
EX-HIG Exercise + high glycemic index diet
 VO_{2max} Maximal oxygen consumption capacity
OGTT Oral glucose tolerance test
FSIVGT Frequently sampled intra-venous glucose tolerance test
FFA Free fatty acid

Managed by Massimo Porta.

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GDR	Glucose disposal rate
Rd	Rate of disposal
HGP	Hepatic glucose production
PPG	Post-loading plasma glucose
IGR ₃₀	Insulin glucose ratio at 30 min
GLUT	Glucose transporter
FAT/CD 36	Fatty acid translocase

Introduction

Pre-diabetes and type 2 diabetes are two varying conditions with worsening degrees of glucose tolerance. Lifestyle modification (i.e., nutrition and physical activity) is the cornerstone of pre-diabetes management aimed at delaying its progression towards type 2 diabetes [1]. Studies have shown that healthy eating patterns such as the DASH (Dietary Approaches to Stop Hypertension) diet, the Mediterranean diet, and modified quality of macronutrient content in diets, are associated with improved glycemia and cardiovascular risk reduction. The American Diabetes Association recommends that a diet with lower glycemic load and lower carbohydrate content is advisable for people with type 2 diabetes [2]. However, their position statement about glycemic index of the diet and its role in delaying the progression of pre-diabetes to type 2 diabetes is still not definitive.

Our group has previously reported that a 3-month low glycemic index diet + exercise (EX-LOG) intervention in conjunction with exercise training results in favorable metabolic outcomes in adults with obesity and pre-diabetes [3]. When compared to a similar study population with a high GI diet + exercise (EX-HIG) intervention, the former individuals significantly improved resting systolic blood pressure, cardiorespiratory fitness (VO_{2max}), and improved fat utilization during exercise [4]. Moreover, physiologically a low GI diet was associated with lower compensatory post-prandial hyperinsulinemia, reduced postprandial glucose-dependent insulinotropic polypeptide (GIP) response and lower extramyocellular lipid content, despite similar improvements in insulin sensitivity. Some of these findings were apparent as early as 7 days into the intervention [5]. However, the role of diet and exercise on glucose-dependent glucose metabolism has not been explored to date.

Acute hyperglycemia has a unique ability to influence carbohydrate metabolism by stimulating glucose uptake and suppressing hepatic glucose production through insulin-independent mechanisms. This action of glucose-mediated glucose metabolism is termed glucose effectiveness (GE) [6]. Type 2 diabetes is patho-physiologically characterized by decreased insulin sensitivity, defective insulin secretion, and blunted GE [7]. Through multiple

experiments, Best et al. estimated the contribution of GE to whole-body glucose disposal after an oral glucose challenge to be ~50% in healthy people, ~85% in individuals who are overweight, and ~99% in individuals with severe insulin resistance [8]. In addition, independent of insulin action, doubling of plasma glucose results in ~50% suppression of hepatic glucose production (HGP) [8], with reductions in the rates of both gluconeogenesis [9] and glycogenolysis [10]. This response of glucose-mediated-suppression of glucose production was proven to be impaired in the presence of elevated plasma free fatty acid concentration (FFA) [11]. Previously, various protocols have measured GE using complex techniques such as a graded hyperglycemic clamp after pancreatic enzyme inhibition [8], and the minimal model approach using frequently sampled intravenous glucose tolerance testing (FSIVGT) [12]. Both of these approaches are invasive and also time and resource intensive. In an attempt to find a surrogate of glucose effectiveness (oGE) via an oral glucose tolerance test (OGTT), Nagasaki et al. developed and validated a mathematical equation to determine GE using an FSIGT, in a Japanese cohort [13]. This equation was further validated in a US population, where it was significantly correlated with FSIVGT-derived GE ($r=0.35$, $P<0.001$), and further, was associated with changes in weight and waist circumference ($r=0.83$ and 0.67 , respectively, $P<0.001$) [14].

GE is one of the modifiable independent predictors of progression to type 2 diabetes along with the insulin secretory response and insulin sensitivity index [15, 16]. Short-term as well as long term exercise training confers modest but significant improvements in GE, which is greater in healthy individuals [17–20], than individuals with type 2 diabetes [21]. However, the effect of the glycemic index (GI) of the diet on exercise-induced changes to GE in individuals with pre-diabetes is unknown. Therefore, we sought to determine if the difference in GI of the diets would result in divergent oGE outcomes in obese individuals who are at-risk for type 2 diabetes.

Materials and methods

Following the response to the study advertisement, a total of 413 individuals underwent screening from August 2009 to December 2012. After obtaining an informed consent, a thorough review of eligible criteria was conducted and 33 older sedentary participants with obesity and OGTT-confirmed pre-diabetes were included to partake in our study. These subjects (17 males/16 females, 65.7 ± 4.3 years, 34.9 ± 4.2 kg m⁻²) were recruited into a 12-week exercise training program (1 h day⁻¹, 5 days week⁻¹ at ~85% of

maximum heart rate i.e., ~70% of VO_{2max}), while being randomized to concurrently receive either a low or high GI diet [3]. All the female subjects were post-menopausal and not on hormone replacement therapy. Individuals on antihypertensive (ACE-I/ARB) or lipid-lowering (statins) therapies were included, following a washout period after drug discontinuation upon consultation with their physicians. Physical activity levels were estimated using the Minnesota Leisure Time Physical Activity questionnaire [22]; and subjects were deemed sedentary if their leisure time activity was $< 300 \text{ kcal day}^{-1}$. This protocol was approved by the Cleveland Clinic Institutional Review Board.

Intervention

Full details of the exercise and diet interventions have been previously reported [3]. In brief, body composition measures including fat mass and fat-free mass were assessed by dual-energy X-ray absorptiometry (model iDXA; Lunar, Madison, WI, USA). Individual VO_{2max} was determined through graded incremental treadmill testing. The test was considered acceptable if at least three of the following criteria were achieved: (1) a respiratory quotient of > 1.10 ; (2) self-determined fatigue; (3) heart rate of ≤ 10 beats per min of age-predicted maximum; (4) leveling off in oxygen consumption with increasing workloads. Plateau VO_{2max} testing was repeated at 4 and 8 weeks during the 12-week period to assure that the appropriate exercise intensity was maintained according

tolerance test (OGTT) was performed, after at least 10 h of fasting, before and after the exercise and diet intervention. Post-testing occurred between 24 and 48 h after the last bout of exercise.

Theory/calculation

Insulin sensitivity was assessed by conducting hyperinsulinemic ($40 \text{ mU m}^{-2} \text{ min}^{-1}$) euglycemic (90 mg dL^{-1}) clamps combined with a [$6, 6\text{-}^2\text{H}_2$]-glucose infusion, before and after the intervention, as described previously [3]. Glucose turnover, which is both insulin-stimulated glucose disposal (GDR) and endogenous glucose production was calculated using the modified Steele equation [24]. Rates of appearance (R_a) and disappearance (R_d) of glucose were calculated during both post-absorptive ($t = -30$ to 0 min) and insulin-stimulated states ($t = 90$ to 120 min). The rate of EGP was calculated as the difference between clamp-derived total R_a and exogenous glucose infusion rate. Since the subjects were fasting overnight before the clamp procedure, the majority of endogenous glucose production was estimated to come from the liver (HGP). Percentage suppression of HGP was calculated as the percentage change of HGP after insulin stimulation relative to baseline. The resting energy expenditure was estimated using an automated system which continuously samples the expired air (V_{max} Encore; Viasys).

oGE was calculated from the OGTT using the Nagasaka equation [13]:

$$\text{oGE (mg dL}^{-1} \text{ min}^{-1}) = \frac{\left\{ [\text{PPG-without insulin and GE}] - [\text{PPG-without insulin/with GE}] \times \left[\frac{2\text{hPG}}{2\text{hPGE}} \right] \right\}}{120}$$

to any possible changes in individual exercise capacity [23]. Appropriate 60-min aerobic exercise interventions, excluding 10-min warm up and cool down times, at ~85% maximum heart rate for 5 days per week, were prescribed and supervised.

Diets were carefully formulated such that all the participants received isocaloric diets ($\sim 1800 \text{ kcal day}^{-1}$) with respect to their individual requirements, determined by indirect calorimetry (model V_{max} Encore; Viasys), and apart from the GI of the diets, macronutrient composition (including fiber) was matched between the groups (EX-LOG vs. EX-HIG: $56 \pm 1\%$ vs. $57 \pm 1\%$ of calories from carbohydrate; $29 \pm 1\%$ vs. $30 \pm 5\%$ of calories from fat; $18 \pm 1\%$ vs. $17 \pm 2\%$ of calories from protein, respectively). To prevent meal repetition, daily menus of the food differed following a 3-day block rotation [5]. Dietary adherence was assessed using a food container weigh back technique on a daily basis, plus counseling by the study dietitian. A 75-g oral glucose

The individual components of this mathematical derivation are: (a) [PPG-without insulin and GE], the post-loading glucose without the action of insulin and glucose which was calculated as: fasting plasma glucose (mg dL^{-1}) + $\frac{[0.75 \times 75,000]}{[0.19 \times \text{BW (kg)} \times 10]}$; (b) 'PPG-without insulin/with GE', the relationship between whole-body insulin action quantified by the disposition index, was obtained from the inverse correlation between $\log_{10} \text{DI}_{(O)}$ and 2-h post-glucose plasma glucose during OGTT (2hPG) across the spectrum of glucose tolerance, where $\text{DI}_{(O)}$ is the oral disposition index; (c) the expected 2hPG (i.e., 2hPG_E) was obtained from the regression between DI_O and 2hPG, and the ratio of $2\text{hPG}/2\text{hPGE}$ constituted the required adjustment factor.

An index of β -cell function, HOMA- β (%), was calculated as $\left(\frac{20 \times \text{Insulin (}\mu\text{U L}^{-1})}{(\text{Glucose (mM)} - 3.5)} \right)$ [25]. An index of glucose-stimulated insulin release, the ratio between insulin and glucose ratio

(IGR₃₀) at 30 min after oral glucose challenge was also calculated [26]. Changes in these indices were correlated with change in GE, with and without subgroup analysis.

Biochemical analyses

Plasma glucose concentrations were measured using YSI 2300 STAT Plus analyzer (Yellow Springs Instruments, Yellow Springs, OH, USA) and plasma insulin concentrations were measured via radioimmunoassay (Millipore, Billerica, MA, USA). Glycated hemoglobin (HbA_{1c}) was measured via nonporous ion exchange high-performance liquid chromatography (G7 HPLC Analyzer; Tosoh Bioscience, San Francisco, CA, USA).

Statistical analysis

Normality of the data was determined using the Shapiro–Wilk test. The continuous data are expressed as means and standard deviations for parametric measures and median and inter-quartile ranges for non-parametric measures. The categorical data are expressed as percentages. Differences between the pre-intervention and post-intervention groups were analyzed for statistical significance using paired

Student *t* tests (parametric) and Wilcoxon-signed rank test (non-parametric) for continuous data and Chi-squared test for categorical data. α was assumed at 0.05. Correlation analyses were performed using Pearson's and Spearman methods and the association between biochemical and anthropometric parameters was evaluated using multivariate linear regression, with and without subgroup analysis, after power transformation. All graphical and descriptive statistical analyses were done using R Studio—version 1.0136 [27].

Results

As previously described, apart from glycemic index (GI) of the diets (low vs. high: 39.8 ± 0.3 vs. 80.0 ± 0.6 au), the macronutrient composition of the diets (including fiber) was essentially similar [4]. Dietary and exercise compliance was > 95% for both the groups. In the low GI group, one subject withdrew midway into the protocol due to a time conflict.

Anthropometric and biochemical measures

Seventeen adult individuals with obesity and prediabetes, with a mean age of 65 ± 3.8 years, median BMI of 34.2 ± 3.4 kg m⁻², had a change in weight of ~ 10 kg after

Table 1 Subject characteristics across the study group

Parameters	EX-HIG		EX-LOG	
	Baseline	Change from baseline	Baseline	Change from baseline
<i>n</i>	17		16	
Age [‡] (years)	64.9 (3.9)		66.9 (4.8)	
Female (%)	48		69	
Ethnicity: Caucasian (%)	76.5		62.5	
Glucose effectiveness (GE: mg dL ⁻¹ min ⁻¹)	1.9 [1.6, 2.3]	0.2 [−0.2, 0.5]	1.9 [1.5, 2.0]	0.3 [0.2, 0.5]*
Weight (kg)	97.6 [89.2, 108.0]	−8.3 [−11.3, −6.8]*	94.6 [88.5, 106.0]	−7.8 [−11.9, −2.6]
BMI (kg m ⁻²)	34.2 [30.9, 37.6]	−2.9 [−4.1, −2.5]*	33.9 [32.0, 36.4]	−2.9 [−3.8, −1.0]*
Body fat (%)	43.2 (6.8)	−10.7 (10.5) [‡]	45.7 (6.2)	5.8 (6.3) [‡]
VO _{2max} (L min ⁻¹)	2.2 [2.1, 2.3]	0.3 [0.1, 0.6]*	2.0 [1.9, 2.2]	0.3 [0.1, 0.7]*
HR _{max} (bpm)	154.4 (11.7)	0.8 (6.1)	150 (11.8)	2.4 (11.2)
Fasting plasma glucose (mg dL ⁻¹)	100 [95, 103]	−7.3 [−12, −1] [‡]	105.0 [101, 114]	−12.6 [−17, −6] [‡]
Two-hour post-load glucose (mg dL ⁻¹)	127 [111, 166]	−7 [−32, 19]	153 [136, 189]	−57 [−104, −39] [‡]
AUC-insulin _{0–120} (a.u)	11,913 (2700)	−5856 (2264)*	15,701 (3315)	−6547 (2292)*
Glucose disposal rate (Rd: mg kg ⁻¹ min ⁻¹)	2.3 [1.7, 3.6]	1.8 [1.1, 2.8] [‡]	2.1 [1.6, 2.9]	1.3 [0.7, 1.9] [‡]
Fasting hepatic glucose production (HGP: mg kg ⁻¹ min ⁻¹)	3.2 [1.9, 3.5]	−0.4 [−1.4, 0.5]	1.9 [1.7, 3.4]	−0.4 [−0.5, −0.1]*
Energy expenditure (kcal min ⁻¹)	6.1 [5.2, 7.0]	1.2 [0.6, 2.3]	5.5 [4.8, 7.1]	1.2 [0.5, 1.5]
HOMA- β (%)	131 (33)	12 (76)	153 (60)	6.6 (41)
IGR ₃₀	1.8 (1.7)	0.5 (1.3)	1.9 (1.5)	0.5 (0.9)

Parametric measures expressed in means (SD); non-parametric measures expressed in median [inter-quartile range]

EX-LOG exercise + low glycemic index diet, EX-HIG exercise + high glycemic index diet, IGR₃₀ insulin glucose ratio at 30 min

* $P < 0.05$; [‡] $P < 0.01$; [‡] $P < 0.001$ —change from baseline

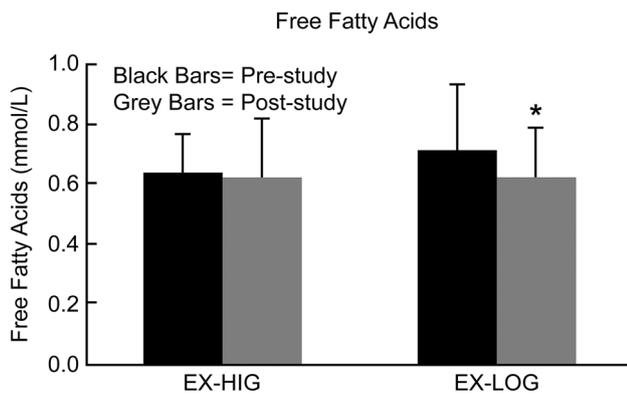


Fig. 1 Comparison of free fatty acid concentration between the study groups. The black bars represent baseline values while the grey bars represent post-intervention values. * $P < 0.05$

the EX-HIG intervention. After the EX-LOG, 16 adults with obesity and prediabetes, a mean age of 67 ± 4.8 years, and a median BMI of $33.9 \pm 2 \text{ kg m}^{-2}$, had a change in weight of $\sim 7 \text{ kg}$. There were significant improvements in fasting serum glucose concentration (~ 7 vs. 13 mg dL^{-1}) and in $\text{VO}_{2\text{max}}$ (2.98 vs. $7.10 \text{ mL kg}^{-1} \text{ min}^{-1}$) with EX-HIG vs. EX-LOG, respectively (Table 1). The FFA concentration decreased by $\sim 28\%$ when compared to baseline, only in the EX-LOG arm ($\Delta\text{FFA}: 0.13 \pm 0.23 \text{ mmol L}^{-1}$) (Fig. 1).

GE and insulin sensitivity measures

With respect to baseline, the improvement in GE was $\sim 12\%$ (Pre vs. Post: $1.9 [1.6, 2.3]$ vs. $2.2 [1.7, 2.7]$) with EX-HIG, while it was $\sim 20\%$ (Pre vs. Post: $1.9 [1.5, 2.0]$ vs. $2.3 [1.9, 2.4]$, $P < 0.01$) with the EX-LOG intervention (Fig. 2).

Insulin sensitivity (GDR) improved significantly with EX-HIG ($\Delta R_d: 1.8 \pm 0.7 \text{ mg kg}^{-1} \text{ min}^{-1}$, $P < 0.05$) and EX-LOG ($\Delta R_d: 1.3 \pm 0.6 \text{ mg kg}^{-1} \text{ min}^{-1}$, $P < 0.05$). Following the low GI diet, fasting (basal) HGP decreased significantly with

Fig. 2 Comparison of glucose effectiveness before and after intervention in EX-HIG (left panel) and EX-LOG (right panel) arms. The red dots represent EX-HIG group and the blue dots represent EX-LOG group. * $P < 0.05$, with respect to baseline. (Color figure online)

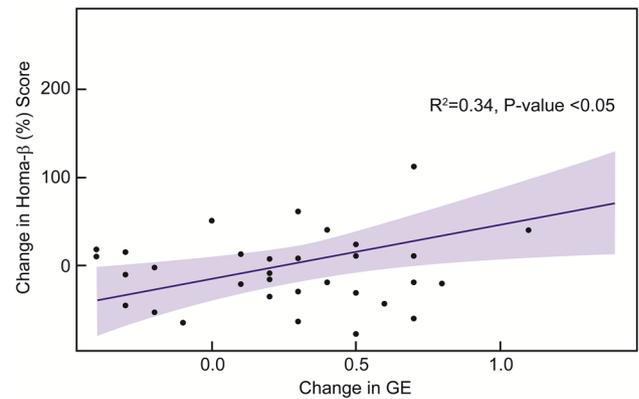
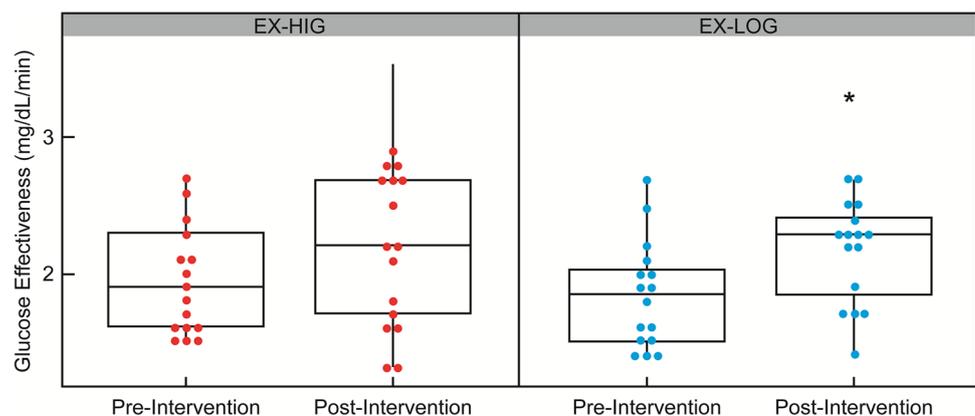


Fig. 3 Relationship between change in GE and change in HOMA- β (%) score. This graph denotes the positive association between change in GE and change in HOMA- β (%) score after the intervention, with respect to baseline. The blue line is the regression line fitting this model and the violet area denotes 95% CI of the regression line. (Color figure online)

respect to the baseline ($\Delta\text{HGP}: -0.59 \pm 0.4 \text{ mg kg}^{-1} \text{ min}^{-1}$, $P < 0.05$).

Correlation analyses

The overall change in oGE with the intervention, in all the participating individuals, showed a significant positive association with the change in HOMA- β score ($R^2 = 0.34$, $P < 0.05$) (Fig. 3). With the EX-LOG intervention, the change in oGE correlated positively with the change in maximal oxygen uptake ($r = 0.5$, $P = 0.05$), resting energy expenditure ($r = 0.56$, $P = 0.03$), IGR_{30} ($\rho = 0.95$, $P < 0.05$) and change in suppression of HGP under insulin-stimulated conditions ($r = 0.54$, $P < 0.05$), and inversely with total glucose area under the curve (AUC) during the OGTT ($r = -0.56$, $P = 0.02$).

Discussion

Glycemic index of foods is classified as either high or low, depending on the crest in plasma glucose concentration elicited after ingestion. Our previous findings suggest that high GI foods may contribute to glucotoxicity by eliciting a sub-optimal response from pancreatic β -cells and incretin-releasing K-cells present in the intestinal villi, in a population at-risk for type 2 diabetes [3]. The current analysis offers insights into an adjunct mechanism through which the glycemic indices of diets might affect yet another emerging physiological mechanism. GE, the ability of glucose to influence its own metabolism, is an important regulator of glucose homeostasis, particularly in pre-diabetes and for people with type 2 diabetes, owing to insulin resistance [28]. While exercise is a known modulator of GE, this study provides novel insight into the impact of the interaction of diet and exercise on GE. Recently, Ahola et al. reported that people with diabetes for longer duration are more likely to follow special diets (such as vegetarian, protein restriction etc.) [29]. There is a clinical need to improve our understanding of the interaction between diet and exercise so that we can explore the effect these special diets may have on glucose metabolism.

Our results show a clear effect of exercise being carried over to the enhancement of GE in the EX-LOG group, while this effect is not evident in the EX-HIG group (Fig. 2). Though both EX-LOG and EX-HIG groups showed significant changes in the GDR, which is predominantly skeletal muscle-mediated glucose uptake, only the EX-LOG resulted in a significant decrement in basal liver glucose production. Increased GE, mediated by an improved FFA profile, in EX-LOG group may have contributed to this decrease in HGP. The significant positive correlation between change in GE and change in suppression of HGP in our data supports a GE-related mechanism. Distinctively, our data also suggest that the high GI diet may suppress the exercise-induced increase in GE.

HOMA- β (%), provides an index of pancreatic β -cell function, and a way to express β -cell capacity to secrete insulin relative to a given glucose load. It is a validated predictor of future development of type 2 diabetes [25]. In our study, using simple linear regression model, we found that GE was independently and positively associated with the HOMA- β score. The data imply that a low GI diet decreases the risk of developing type 2 diabetes in a high-risk population possibly by improving GE-associated pancreatic β -cell function. Moreover, GE after EX-LOG intervention correlated with decreased AUC at 2-h of post-load glucose and improved IGR₃₀, implying that GE may also decrease the stress on pancreatic β -cells. Further, the change in GE after low GI foods was also associated with a better physiological and biochemical profile while high GI was not, even though

exercise training and total caloric intake was similar for both interventions. This provides additional evidence that a low GI diet would facilitate the effects of exercise training on GE and β -cell function, whereas the high GI diets tend to oppose this effect.

One possible explanation for the observed effect is that the chronic compensatory hyperinsulinemia with habitual high GI intake could induce accumulation of fatty-acid derivatives that would impair insulin receptor signaling, thereby eliciting a sub-optimal GLUT4 receptor translocation to the plasma membrane, in response to the exercise [30]. More in-depth evaluation of the possible molecular mechanisms (including skeletal GLUT1 content, GLUT4 content and FAT/CD36 gene expression levels) are underway [31, 32].

A potential limitation to our study is the use of an oral surrogate of GE (i.e., oGE), instead of the gold standard graded hyperglycemic pancreatic clamp. However, the use of the current approach is more feasible and yields validated data, as shown by Nagasaka et al. and Weiss et al. [13, 14]. In addition, the smaller sample size in our study could make it hard to extrapolate the findings to the general population. Another limitation to the current approach is the inability of the model to delineate the components of GE, i.e., its impact on endogenous glucose production and on whole-body glucose uptake, because of the absence of a labelled tracer during the OGTT. However, the use of OGTT measures makes this model physiological and more applicable to our daily lives.

Conclusions

In conclusion, the enhancing effect of exercise on GE might be influenced by the GI of the foods, with low GI being facilitative and high GI being unfavorable. Individual changes in GE are associated with physiological and biochemical improvements after the EX-LOG intervention. These findings may help caregivers to better counsel their patients regarding adoption of a healthier lifestyle towards the primary prevention of cardio-metabolic disorders. Future long-term studies are needed to determine the impact of diet and exercise on mitigating the risk of developing type 2 diabetes.

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Author contributions AH, CF and JPK generated the data and wrote the manuscript. TPJS, JMH, KRK and HB helped generate the data,

reviewed/edited the manuscript and approved the final version. JPK is the guarantor of this work and has full access to the all the data in the study.

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Data Availability The datasets generated during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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