

Review Article

Enhancing Exercise Responsiveness across Prediabetes Phenotypes by Targeting Insulin Sensitivity with Nutrition

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Exercise is a cornerstone therapy for chronic diseases related to multiorgan insulin resistance. However, not all individuals show the anticipated improvement in insulin sensitivity following exercise and these individuals are considered exercise resistant. Caloric restriction is an approach to enhance the effect of exercise on increasing peripheral and hepatic insulin sensitivity, as replenishing expended calories blunts these benefits. Alternatively, restricting carbohydrate intake, independent of energy balance, following exercise provides an additive effect on peripheral insulin sensitivity when compared to refeeding carbohydrate. Although carbohydrate composition modulates insulin sensitivity, few have studied effects of low glycemic index or whole-grain diets following exercise across prediabetes phenotypes on insulin sensitivity. Herein, we propose the novel hypothesis that the combination of individualized nutrition therapy and exercise should be based on the clinical pathology of prediabetes to overcome exercise resistance and improve responsiveness in people at risk for type 2 diabetes and cardiovascular disease.

1. Introduction

Approximately 382 million adults worldwide have type 2 diabetes (T2D), and this figure is projected to rise to 592 million by the year 2035 [1]. Prediabetes is characterized by blood glucose levels above normal but below the diagnostic criteria for T2D [2]. The etiology of prediabetes is primarily skeletal muscle, liver, and/or adipose tissue insulin resistance that, in time, promotes oversecretion of insulin from the β -cell and results in pancreatic exhaustion that leads to severe hyperglycemia [3].

Skeletal muscle insulin resistance is primarily responsible for impaired glucose tolerance (IGT; 2 hr postprandial glucose > 140 mg/dL). In contrast, hepatic insulin resistance manifests mainly as impaired fasting glucose (IFG; fasting plasma glucose > 100 mg/dL) because glucose production is excessive despite normal insulinemia [4]. Individuals with both IFG and IGT (i.e., IFG+IGT) have peripheral and hepatic insulin resistance. Obesity is considered a chief factor

promoting this insulin resistance, and many individuals with IFG and/or IGT are advised to lose approximately 5–10% of body weight by consuming a low-fat diet and participating in at least 150 min/week of moderate or 75 min/week of vigorous intensity exercise [5]. However, there is substantial intersubject variability for glycemic control [6, 7], cardiometabolic health [8, 9], and skeletal muscle hypertrophy [10] in response to lifestyle intervention, despite exercise intensity influencing these fitness-related insulin sensitivity adaptations [11]. Those who respond with little improvement, or even with adverse response, are often termed “nonresponders” or “exercise resistant.” With regard to prediabetes, individuals with IFG + IGT have attenuated insulin sensitivity responses to high-volume (300 min/wk)/high-intensity (85% HR_{max}) exercise with approximately 7% weight loss treatment as compared to IFG or IGT alone [6, 7]. This phenomenon represents a specific case of intersubject variability in response to a high dose of exercise. Interestingly, ad libitum changes in diet behavior were recently suggested

to have tissue-specific effects on insulin sensitivity [12]. As IFG generally develops due to hepatic insulin resistance and IGT emerges from skeletal muscle insulin resistance, we propose the novel hypothesis that applying individualized dietary prescription may enable the insulin-sensitizing effects of exercise in exercise-resistant individuals based on the underlying hyperglycemic phenotype [6, 7, 9].

This review will examine the potential for diet to augment the benefits of exercise on glucose regulation in people with insulin resistance in the liver and skeletal muscle. In particular, attention will focus on the impact of energy balance, carbohydrate balance, and carbohydrate type (i.e., low glycemic index (GI) and whole grain) in conjunction with exercise on multiorgan insulin resistance and glycemic control. Acute exercise interventions consist of 1–10 days to reflect metabolic responsiveness, while chronic (~>8 weeks exposure) exercise studies are used to understand adaptations to the stimuli. These exercise conditions are discussed separately because insulin sensitivity effects may differ based on the length of exposure.

2. Energy Deficit

2.1. Acute Exercise. Energy deficit following acute exercise contributes to increased postexercise insulin sensitivity. In fact, an energy deficit of 6.5 kcal/kg body weight following an acute exercise bout resulted in a 22% lower postprandial insulin incremental area under the curve (AUC) during an oral glucose tolerance test (OGTT) compared with an 11% decrease when expended calories were replenished [13]. This suggests that approximately 50% of the exercise effect on insulin sensitivity is due to the exercise-induced energy deficit. Although use of an OGTT limits the ability to discern whether skeletal muscle or liver is responsible for the improvement, earlier work using clamp or stable isotope approaches confirm that energy deficit is at least partially responsible for increased insulin sensitivity. Assali et al. prescribed hypocaloric diets in two groups of obese individuals by caloric restriction of 33 or 66% of the habitual energy intake [14]. Peripheral insulin sensitivity as measured by the euglycemic clamp increased significantly in the first week of the intervention, before any documented change in weight. In 2 subsequent weeks when subjects were prescribed an isoenergetic diet, the same improvements in insulin sensitivity were lost. Consistent with these observations, Black et al. studied the effects of an energy deficit (500 kcal/day) induced by 6 days of exercise training on isotope-derived insulin sensitivity in overweight and obese adults in comparison to a group who had calories replenished following exercise [15]. After training, the energy deficit intervention increased peripheral glucose disposal and suppressed hepatic glucose production compared to energy repletion. In another acute study, a 10-day energy deficit via either moderate aerobic exercise training or a low-calorie diet (50% of kcal needed to maintain energy balance) in obese, IGT, and T2D subjects significantly increased insulin action as determined by a modified hyperglycemic clamp [16]. Despite similar energy deficits, exercise training had a significantly greater effect on improving insulin action than the low-calorie diet.

Together, these studies support that energy deficit is an important mechanism accounting for increased skeletal muscle and hepatic insulin sensitivity, but that exercise training confers additional improvement. Thus, combining exercise with diet-induced energy deficit could be a manner of alleviating exercise resistance in groups such as IFG + IGT, but this remains to be tested.

2.2. Exercise Training. Long-term studies ranging from 6–12 months report that exercise-induced energy deficit is responsible for increasing insulin sensitivity. Weiss et al. demonstrated that energy deficit via caloric restriction or exercise after 12 months improved insulin sensitivity comparably [17]. This is consistent with work by Larson-Meyer et al. showing that when energy deficit was held constant through 25% caloric restriction or 12.5% caloric restriction plus 12.5% energy expenditure from aerobic exercise, there was no difference between groups in skeletal muscle insulin sensitivity improvements [18]. Moreover, in obese, nondiabetic African American women who underwent 14 weeks of high-intensity interval training (HIIT) with a weight-maintenance diet [19], there was no significant increase in insulin sensitivity when calories were refed. Collectively these studies suggest that energy deficit is important for explaining the improved insulin sensitivity seen with chronic exercise training. Indeed, when lean, obese, and T2D men underwent 12 weeks of aerobic exercise training and were refed sufficient calories (55% carbohydrate, 21% fat, and 24% protein) to maintain body weight, no group experienced improvements in peripheral insulin sensitivity as measured by the clamp, despite increased oxidative glucose disposal [20]. Nonetheless, basal hepatic glucose production was reduced in subjects with T2D following exercise plus diet, indicating an independent effect of exercise on liver glucose metabolism in people with T2D. More recent work suggests that an energy deficit of about 700 kcal/day by either restricting caloric intake (diet-induced weight loss) or 60 min/day of moderate intensity aerobic exercise (exercise-induced weight loss) resulted in similar increases in glucose tolerance and nonoxidative glucose disposal [21]. These findings are similar to those of Solomon et al. [22], who compared a eucaloric diet plus exercise (i.e., energy deficit by exercise) or a hypocaloric diet plus exercise (i.e., diet-imposed 500 kcal/day deficit plus exercise-induced energy deficit) in older, obese, sedentary adults. Individuals in the hypocaloric diet group lost approximately 4 kg more weight compared with people in the eucaloric group. Clamp-derived peripheral insulin sensitivity improved similarly in both groups following the 12 weeks of aerobic exercise training regardless of eucaloric or hypocaloric diet, suggesting that above a given threshold of weight loss, there may be no further improvement in insulin sensitivity. However, subsequent work by the same group showed that hepatic insulin sensitivity improved to a greater extent following exercise training with hypocaloric diet than with a eucaloric diet during lipid-infused conditions [23]. This suggests that in addition to exercise, calorie restriction may protect the liver from obesity-driven insulin resistance more so than training alone, despite comparable peripheral insulin sensitivity. These findings may suggest that people with

hepatic insulin resistance derive more benefit by focusing on energy deficit than those people with IGT alone [23].

A confounding factor when interpreting the collective findings from the effects of acute and long-term energy deficit on insulin sensitivity is that a carbohydrate deficit is often induced concurrently. This raises the possibility that carbohydrate deficit (e.g., low-glycogen concentrations), and not energy deficit per se, regulates insulin sensitivity postexercise (see Carbohydrate Availability). Further work awaits investigation to elucidate the optimal nutrition program for maximizing improvements in hepatic and/or skeletal muscle insulin resistance during exercise interventions across the prediabetes phenotypes.

3. Carbohydrate Availability

3.1. Acute Exercise. Skeletal muscle glycogen concentration is a driver of insulin-stimulated glucose uptake [24], and exercise and dietary carbohydrate intake both affect muscle glycogen. In healthy young men, exercise-induced glycogen depletion combined with dietary carbohydrate restriction promotes insulin sensitivity [25], but no studies have tested this effect in subjects with hyperglycemia. Nonetheless, Holtz et al. [26] studied overweight, sedentary, normoglycemic adults and found that carbohydrate restriction after moderate exercise increased nonoxidative glucose disposal during glucose infusion to a greater extent than carbohydrate replenishment. This higher degree of carbohydrate restriction was strongly correlated with enhanced insulin action, suggesting that exercise-mediated glycogen depletion modulates the insulin-stimulated effect on skeletal muscle glucose uptake. In addition to the degree of carbohydrate restriction, the timing of nutrient intake may affect peripheral insulin sensitivity. After an exercise session, insulin action improved to the greatest extent when subjects were refed the expended calories and carbohydrate immediately after the exercise bout, as opposed to immediately before or 3 hr after exercise [27]. However, insulin-mediated hepatic glucose production was significantly suppressed with preexercise or 3 hrs delayed feeding compared with immediately postexercise feeding. Although these findings may not generalize to individuals with hyperglycemia, as the subjects tested were fit and of normal weight, the results suggest that the timing of energy and/or carbohydrate intake relative to exercise may alter whether peripheral or hepatic insulin sensitivity are most affected. If true in individuals with prediabetes, this would have implications for augmenting insulin sensitivity using exercise and nutrition prescriptions categorized by prediabetes phenotype.

To gain insight into the importance of carbohydrate restriction on enhancing exercise-induced insulin sensitivity, it is necessary to compare energy deficit and replenishment models that are matched for carbohydrate intake [25, 26, 28]. Studies on dietary energy deficit cannot distinguish whether exercise-induced insulin sensitivity is augmented by global calorie reduction or a specific effect of carbohydrate deficit. Those that compare postexercise dietary energy restriction plus carbohydrate balance, energy restriction plus carbohydrate restriction, and energy restriction plus carbohydrate

balance are useful for understanding the importance of carbohydrate. They establish that carbohydrate is a key dietary variable for augmenting insulin sensitivity following exercise [29, 30]. Nevertheless, energy deficit even with carbohydrate replenishment enhances fat oxidation [29, 30], which may be advantageous for improving clamp and OGTT-derived insulin sensitivity during periods of energy deficit [31–33]. Similar to the study of Holtz et al. [26], greater improvement in insulin sensitivity coincided with greater reductions in skeletal muscle glycogen [30]. Given that chronic hyperglycemia attenuates skeletal muscle glycogen utilization during exercise [34–36], this observation of glycogen depletion could be important for individualizing exercise prescription if these results hold true in adults with T2D or IFG+IGT. Furthermore, this may explain to some extent why people with IFG+IGT appear exercise resistant and respond to exercise with smaller rises in insulin sensitivity [37]. Thus, adults with IFG+IGT could benefit from restricted postexercise carbohydrate intake of approximately 3 to 12 hrs [27, 30]. Further work is required to identify specific postexercise carbohydrate manipulations to increase insulin sensitivity among different prediabetes phenotypes.

Since insulin suppresses lipolysis via adipocyte insulin action, diets high in carbohydrate could reduce circulating lipids (barring high dietary fat intake) and diminish lipid-induced impairments on hepatic and/or skeletal muscle insulin sensitivity. This may be important for individuals with IGT, who tend to have more severe adipose insulin resistance than individuals with IFG [38]. Carbohydrate restriction after an exercise bout may enhance adipocyte insulin sensitivity. Harrison et al. [39] reported that circulating triglycerides (TG) were lower and free fatty acids (FFA) were higher during an oral fat tolerance test (OFTT) after an exercise bout and carbohydrate restriction. The effect was absent when carbohydrate was refed to replenish the exercise expenditure, suggesting adipocyte insulin sensitivity, was enhanced by dietary restriction after exercise. While muscle glycogen was substantially reduced by carbohydrate restriction, the study design makes it unclear whether carbohydrate deficit per se or energy deficit was responsible for reducing circulating TG. In either case, other work indicates that energy deficit decreases circulating TG in response to a high-fat meal thereby minimizing deleterious effects of lipids on insulin action [40]. To date, few data exist examining the impact of refeeding with or without carbohydrate on lipid availability as a result of insulin sensitivity. Further work is needed to understand the interaction among exercise, carbohydrate restriction, insulin sensitivity, and lipid availability, particularly in individuals with IGT who have adipose insulin resistance.

A final consideration with regard to restricting carbohydrate intake is that limiting one nutrient could be compensated by increased intake of another, such as fat. High dietary fat intake is thought to decrease insulin-stimulated skeletal muscle glucose uptake because of a rise in circulating lipids [41–44]. However, exercise may offer some protection. Several studies [45, 46] suggest that a 90 min aerobic exercise bout enhances peripheral and hepatic insulin sensitivity regardless of high- or low-fat feeding after the bout. Since

skeletal muscle lipid oxidation capacity is correlated with insulin sensitivity in subjects with a high VO_2peak and high IMTG content [47], these subjects' tolerance to high-fat meals may be partly explained by their aerobic fitness ($\text{VO}_2\text{peak} = 55.5 \pm 1.6 \text{ mL/kg/min}$) [45] or the high oxidative capacity of females [46]. Further studies are needed to understand effects in clinical populations. Nonetheless, carbohydrate intake and muscle glycogen content were similar across conditions in these studies, thereby reinforcing the hypothesis that carbohydrate, and not fat, is a key dietary variable for enhancing exercise-induced insulin sensitivity in short term.

3.2. Exercise Training. While acute studies suggest that exercise with carbohydrate restriction may be effective for enhancing the insulin-sensitizing effect of exercise at the level of skeletal muscle and the liver, it is currently unknown whether this nutritional strategy is effective in conjunction with chronic exercise training in clinical populations. Subsequently, we can only speculate that since individuals with IFG + IGT tend to have blunted insulin sensitivity and fuel selection exercise responses to training [6, 7], carbohydrate restriction could be a strategy to enhance exercise-related mitochondrial adaptations in this population that relate to insulin sensitivity [48]. The mechanism by which low carbohydrate availability confers metabolic adaptation has been shown to act through targeting glycogen depletion to upregulate mitochondrial oxidative enzymes (e.g., citrate synthase, β -HAD) involved in glucose tolerance and insulin action [49, 50]. Further work is needed to determine whether exercise training with carbohydrate restriction is feasible in individuals across the prediabetes phenotypes.

4. Glycemic Index

4.1. Acute Exercise. The glycemic index (GI) of a food is characterized by the resulting blood glucose excursion with reference to a standardized meal (e.g., white bread or glucose) [51]. On the other hand, the glycemic load (GL) is determined by the GI of the food multiplied by the amount of carbohydrate (i.e., grams) in that serving, also described by the area under the curve of the GI response. It is worth acknowledging, however, that GI and GL are independent of dietary energy, which has been an important topic of this review. Nevertheless, the purpose of a low-GI or low-GL diet is to manage circulating glucose levels (and by association, insulin levels), which in turn, may contribute to healthier body weight, reduced appetite cravings, and improved cardiometabolic health [51, 52]. Although few studies have systematically compared the effect of low versus high GI food following an acute bout of exercise on insulin sensitivity, it should be noted that many of the acute exercise studies examined in this review utilized a high content of simple carbohydrates, which have a high GI index. In one of the few acute studies conducted, Solomon et al. [53] examined older, obese adults after 7 days of moderate intensity aerobic exercise together with a low- or high-GI diet. Exercise combined with low- and high-GI diets enhanced insulin-stimulated glucose disposal and hepatic glucose production

(markers of peripheral and hepatic insulin sensitivity). Since these two diets improved insulin sensitivity in both tissues, further work is warranted to determine whether IFG, IGT, and IFG + IGT phenotypes respond differently to each diet. Although the low-GI diet did not improve insulin sensitivity more than high GI following acute exercise, the low-GI group reduced systolic blood pressure to a greater extent. Thus, a low-GI diet with exercise may contribute to short-term cardiovascular benefits, presenting a possible strategy to mitigate cardiovascular disease if exercise is performed regularly. This may be clinically important for the prediabetes phenotypes since individuals with IFG + IGT have higher CVD risk than those with IGT or IFG [54].

4.2. Exercise Training. Exercise training and a eucaloric low-GI diet have been suggested to synergistically enhance glucose regulation in older adults with prediabetes [55]. Despite comparable improvements in peripheral and hepatic insulin sensitivity, exercise training combined with a low-GI diet can preserve β -cell function and reduce insulin secretion demand to a greater extent than a high-GI diet [56]. Preserving β -cell function is relevant to all three prediabetes phenotypes (IFG, IGT, and IFG + IGT), since pancreatic dysfunction is differentially implicated in the progression to T2D [57]. On the other hand, Malin et al. [58] showed that 12 weeks of either a low- or high-GI diet and supervised exercise training was effective in lowering HbA_{1c} and body fat as well as increasing peripheral insulin sensitivity in adults with metabolic syndrome, without change in resting fat oxidation. Consistent with this observation, a low-GI food consumption combined with increased walking in adults with T2D resulted in reductions of HbA_{1c} that were similar to increased walking alone [59]. When drawing on these observations, there does not appear to be clear evidence that a eucaloric low-GI diet confers benefit above that of a high-GI diet when combined with increased physical activity and/or exercise training. Additional research is needed to understand differential responses in each prediabetic phenotype to better understand personalizing diets with exercise on insulin sensitivity and/or secretion.

5. Whole Grains

To date, there are no systematic acute or long-term exercise interventions combined with whole-grain consumption examining effects on insulin sensitivity in hyperglycemic individuals. However, epidemiological data suggest that dietary whole-grain intake (e.g., oats and barely) is associated with a lower incidence of T2D compared with refined-grain intake [60]. Whole-grain consumption ($\sim 30\text{--}60 \text{ g/d}$) may also reduce the risk of progression from normal glucose tolerance to prediabetes [61]. Indeed, Kirwan et al. [62] recently demonstrated that 8 weeks of whole-grain diet (consisting of mainly wheat and rice) feeding decreased HbA_{1c} , fasting insulinemia, and insulin resistance (HOMA-IR) in overweight/obese subjects. The reason whole-grain intake lowers T2D risk is an area ready for investigation as preliminary work suggests that short-chain fatty acid release in the gut mediates the effect of whole-grain (bran and germ

TABLE 1: Summary of exercise plus diet effects compared with preintervention.

	Insulin-stimulated muscle glucose uptake	Nonoxidative glucose disposal	Glycogen concentration	Hepatic insulin sensitivity	Fat oxidation
Caloric restriction	↑ [15, 22]	↑ [15]	↔ [30]	↓ [16]	↑ [22, 29, 30]
Caloric replacement	↑ ↔ [15, 20–22, 75]	↓ ↔ [15, 20]	↔ [30, 39, 46]	↑ ↔ [15, 20]	↑ ↔ [13, 19, 30]
CHO restriction	↑↑ [26, 30]	↑↑ [26]	↓ [30, 39]	↔ [26]	↑ ↔ [30]
CHO Replacement	↔ [30]	↑ ↔ [26, 27]	↔ [30]	↔ [27]	↑ [27]
Low GI	↑ [56]	↑ [52]	?	↑ [52]	?
High GI	↑ [52]	↑ [52]	?	↑ [52]	?
Whole grain	?	?	?	?	?
Refined grain	?	?	?	?	?

↑ indicates an increase. ↓ indicates a decrease. ↔ indicates no substantial change. ? indicates inconsistent findings or no available data across studies. ↑↑ indicates a substantial change.

with high fiber) intake on clamp-derived insulin sensitivity in overweight adults with or without metabolic syndrome [63]. This suggests that whole-grain intake may improve skeletal muscle glucose uptake or reduce hepatic glucose production regardless of the metabolic derangement. However, whole grains have little effect on rates of meal glucose appearance from the gut in response to a standard OGTT with the dual-tracer technique [64, 65]. A single meal consisting of whole grains (barley-based meals rich in the soluble fiber β -glucan) results in better glycemic control than refined grains due to lower hepatic glucose production [65]. In addition, longitudinal data support that whole-grain consumption (rye bread based) may result in improved β -cell function [66]. It is worth recognizing though that dietary fiber is often associated with whole-grain intake and has shown independent effects on insulin sensitivity [67, 68]. Collectively, these studies support that whole-grain intake can improve peripheral and hepatic insulin sensitivity, along with pancreatic function. The results are thus relevant to IFG, IGT, and IFG+IGT populations, and particular attention should be paid to IFG+IGT since these individuals are most at risk for progression to T2D and may benefit from the combined peripheral and hepatic effects of whole-grain intake. However, whether adding whole grains and/or fiber augments, exercise effects above remain to be seen. This could be of clinical interest since exercise is a significant variable when studying the relationship between fiber intake and insulin resistance [67]. Future research is needed to examine responses in each obese prediabetic phenotype to the interaction between whole grains with acute and long-term exercise on insulin sensitivity for T2D prevention/treatment.

6. Conclusions

Modifying dietary energy and nutrient intake is an appropriate tool to enhance the effectiveness of exercise on insulin sensitivity. Various dietary strategies appear to have independent effects on targeting skeletal muscle versus hepatic insulin sensitivity (Table 1). For instance, inducing an energy deficit improves skeletal muscle and hepatic insulin

sensitivity following acute and chronic exercise interventions, which has implications for individuals with IFG, IGT, and IFG+IGT. Carbohydrate restriction is primarily responsible for depleting and maintaining low skeletal muscle glycogen, which enhances peripheral glucose uptake further than energy deficit with carbohydrate balance. Individuals with IGT, and especially IFG+IGT (as this group is more resistant to insulin sensitizing effects of exercise [6, 7]), may benefit from restricting carbohydrate intake following exercise bouts. Increased fasting fat oxidation is also consistently observed after exercise with calorie and/or carbohydrate restriction, suggesting that enhanced mitochondrial reliance on fat may contribute to improved insulin sensitivity. Effects of low- versus high-GI carbohydrates are unclear, but the literature supports that exercise followed by high-GI carbohydrate intake increases pancreatic insulin secretion. The pancreas is thus potentially subjected to additional burden in order to maintain normal glycemia. This is undesirable in IFG, IGT, and IFG+IGT phenotypes as pancreatic β -cell dysfunction contributes in the progression to T2D [69]. Whether whole grains modulate exercise adaptation also remains to be seen. This is important as nutritional interventions suggest that adherence to low or high carbohydrate-based diets overtime may be most important for weight loss and glycemic control [70, 71].

A substantial number of the studies on interaction of nutrition and exercise for insulin action have been conducted in nonclinical populations. Clinical trials are needed to determine the efficacy of diet plus exercise for T2D prevention, particularly across the prediabetes phenotypes. Although individuals are often advised to consume nutrients at specific times before and after exercise to stimulate physiological adaptation and maximize athletic performance [72–74], the implication of nutrient composition and timing for individuals with IFG, IGT, and IFG+IGT remains largely unknown. Furthermore, no data exist examining the interaction between exercise intensity and nutrient composition and timing. These are significant knowledge gaps to fill since the pathophysiology of prediabetes differs among the clinical phenotypes. Addressing these questions will eventually allow

individualized diet and exercise prescription and inform clinical and public health recommendations for optimizing the prevention and/or delay of T2D onset.

Conflicts of Interest

All authors declare that they have no competing interests.

Authors' Contributions

Julian M. Gaitan and Steven K. Malin shared responsibility for writing the manuscript. Arthur Weltman reviewed and provided edits to the manuscript.

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