REVIEW

The sliding set-point: how insulin and diet interact to explain the obesity epidemic (and how to fix it)

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Purpose of review
The current approach to weight loss (intentional energy deficit) is difficult to implement and sustain, and rarely leads to successful long-term weight loss maintenance. The aim of this article is to review recent literature on the role of insulin in obesity propensity, and by extension, the effectiveness of carbohydrate restriction in facilitating weight loss, with particular attention to individual variability in patient response.

Recent findings
A genetic signature for insulin secretion predisposes to elevated BMI. A genetic signature for insulin resistance is a marker for impaired fat storage, is associated with relative leanness, and predisposes to cardiometabolic disease. The largest randomized weight-loss trial ever conducted to examine insulin/diet interactions revealed no interactive effect of insulin phenotype with diet composition on body weight in the context of energy restriction. However, smaller studies revealed unique effects of carbohydrate restriction on energy partitioning that are not reflected in body weight; that is, preferential loss of total and ectopic adipose tissue. Carbohydrate-restricted diets are associated with greater adherence, and with greater total and resting energy expenditure.

Summary
For patients with a predisposition to high insulin secretion, carbohydrate restriction may facilitate long-term reductions in body fat, perhaps by reducing hunger, maintaining energy expenditure, and promoting adherence.

Keywords
carbohydrate restriction, diet, ectopic lipid, energy expenditure, insulin resistance, insulin secretion, insulin sensitivity, visceral adipose tissue

INTRODUCTION

Although obesity is highly heritable, the physiologic basis for this heritability is not clear. Further, genetic variation alone cannot explain the increase in obesity over the past ~50 years. We suggest that genetic variation in the insulin axis (insulin secretion or insulin sensitivity) comprises at least a portion of obesity heritability. Insulin is an anabolic hormone with strong lipogenic actions. Regular injections of insulin cause fat gain, as do insulin-sensitizing drugs. It is plausible that individual variation in insulin action contributes to obesity. A corollary of this hypothesis is that lowering insulin secretion via restriction of dietary carbohydrates would facilitate weight loss in patients with insulin-driven obesity. We summarize here data supporting the concept that carbohydrate restriction has beneficial effects on weight loss for specific groups of individuals who suffer from insulin-dominated metabolic phenotypes.

INSULIN SENSITIVITY AND INSULIN SECRETION

Insulin sensitivity has been implicated in weight gain in several prospective or longitudinal studies. Free-living, weight-reduced (formerly obese) women gained a greater amount of body fat over 1 year if they were relatively more insulin sensitive at baseline [1]. Similarly, greater baseline insulin sensitivity was associated with greater weight gain over an average of 3.5 years in nondiabetic Pima Indians [2]. In this study, the percentage weight

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KEY POINTS

- Risk for both obesity and metabolic disease is likely to be genetic, with manifestation dependent upon diet.
- Variation in genes affecting insulin secretion is associated with risk for obesity, whereas variation in genes affecting adipocyte differentiation in peripheral adipose tissue is associated with insulin resistance and risk for cardiovascular disease and type 2 diabetes.
- For patients with a genetic risk for obesity related to insulin secretion/action, a low glycemic or carbohydrate-restricted diet may facilitate weight loss.
- Carbohydrate-restricted diets may have effects on hunger/satiety and energy expenditure that facilitate weight loss maintenance.
- The body weight 'set-point' is diet dependent.

change per year was associated with the glucose disposal rate during the euglycemic clamp. In moderately obese women, a relatively greater improvement in insulin sensitivity following weight loss was associated with greater weight regain over 12 and 18 months [3]. Naturally occurring conditions when insulin sensitivity is elevated, such as phosphatase and tensin homolog haploinsufficiency [4] and early pregnancy [5], are associated with weight gain. In the Nurses' Health Study, circulating adiponectin, a marker for terminal adipocyte differentiation and insulin sensitivity, was predictive of weight gain [6].

The importance of insulin sensitivity on weight gain has to be interpreted in the context of insulin secretion, and vice versa. This concept was beautifully illustrated in a study of offspring of parents with type 2 diabetes [7]. Over an average of 17 years, the interaction of insulin sensitivity and the acute insulin response to glucose (AIRg) predicted the greatest weight gain (Fig. 1). In this sample, AIRg (but not insulin sensitivity) had an independent main effect. In contrast, in nondiabetic African-American women, who as a group display high AIRg, insulin sensitivity (but not AIRg) predicted weight gain [8].

DIET AND THE SLIDING SET-POINT

Although inherent variation in insulin-related measures may affect body fat accrual, it cannot explain the ever-escalating prevalence of adult obesity, which according to the most recent data available, is 39.6% [9]. The increase in obesity over the past several generations is most likely due to a shifting of the set-point at which body fat is defended in

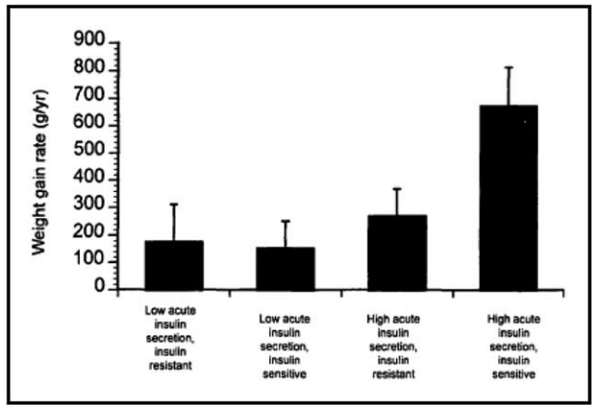

FIGURE 1. Synergistic effect of insulin sensitivity (S_I) and the acute insulin response to glucose (AIRg) on free-living weight gain over a mean follow-up period of 17 years [7].

response to environmental factors that interact with insulin. This has led to the hypothesis that the increase in highly processed carbohydrate food products over the past ~50 years has contributed to the obesity epidemic [10]. Superimposing genetic susceptibility on a food supply with steadily increasing processed carbohydrates could explain the upward ratcheting of the American BMI (Fig. 2). In Fig. 2, women appear to show a larger increase in BMI than men as carbohydrate intake increased, a difference that may be explained by higher insulin sensitivity in women [11], and effects of estrogen on beta cell mass, insulin secretion, and insulin sensitivity [12]. Thus, although circumstantial, the existing epidemiological data support a potential role for increased dietary carbohydrates as providing the environmental stimulus for a gene-by-environment interaction in determining increased BMI over the past ~50 years.

INSULIN PHENOTYPE BY DIET INTERACTIONS

The concept that insulin secretion affects body weight in a diet-specific manner was first illustrated in a study of obese young adults randomized to high versus low glycemic diets [13]. The diets were not energy restricted, and in all participants combined, the two diets had similar albeit modest effects on body weight over 18 months. However, when the participants were stratified by insulin concentration 30 min after glucose ingestion ('insulin-30'; 'high' versus 'low'), weight loss was strikingly greater with the low glycemic diet within the 'high insulin' group, and was maintained at 18 months (Fig. 3). Because food intake was *ad libitum*, the results imply that weight loss occurred spontaneously in the high insulin group in response to a change in body

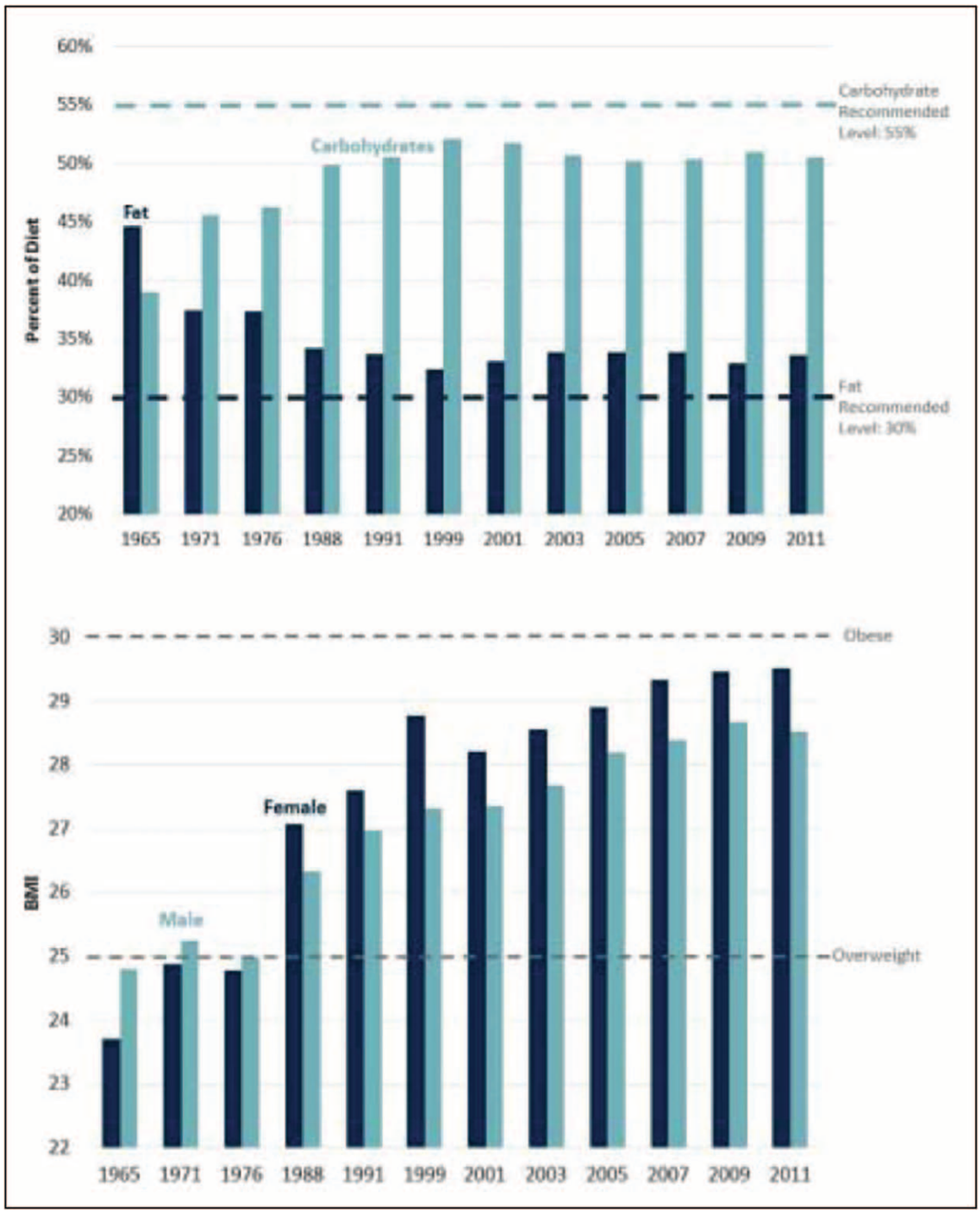

FIGURE 2. National Health and Nutrition Examination Survey (NHANES) data illustrate parallel increases in diet percentage carbohydrate and BMI in the US between 1965 and 2011 [9].

weight regulatory factors induced by the low glycemic diet. And, because weight loss was maintained, this observation suggests that the body weight set-point in the high insulin group was reset to a new, lower, level when the individuals consumed the low glycemic diet. Phenotype-by-diet interactions also have been reported in nondiabetic African-American women, who as a group display high AIRg. Over one year following intentional weight loss, weight regain was predicted by the combination of insulin sensitivity with diet glycemic load. Those women with the highest insulin sensitivity and the highest

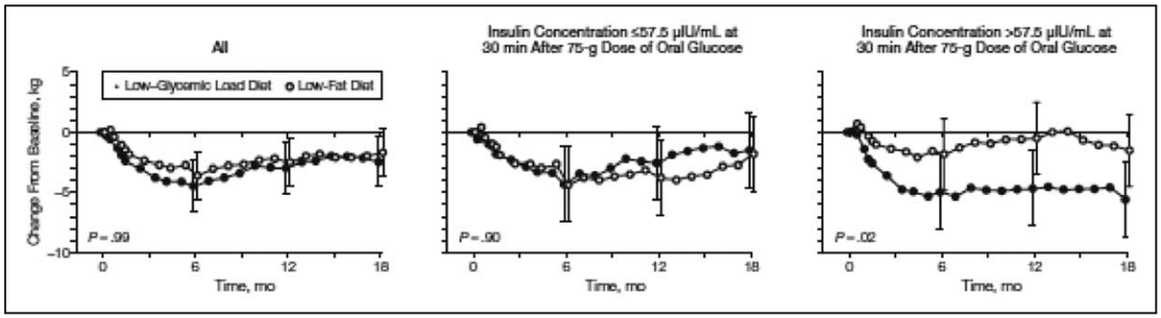

FIGURE 3. Participants with higher insulin secretion lost more weight on a low versus high glycemic ad-libitum diet over 18 months [13].

glycemic load diet gained the most weight [8] (Fig. 4). Other studies support the concept of an insulin-by-diet interaction regarding weight loss [14–16]. Taken together, these observations suggest that different populations have different 'drivers' for body weight, perhaps based on population characteristics (e.g., family history of diabetes, high insulin secretion, or constitutively high AIRg). Further, these 'drivers' may interact with other factors, including diet. Thus, as a minimum, body weight appears to be predicted by a three-way interaction: insulin concentration × insulin sensitivity × diet glycemic load. This complex interplay amongst predisposing variables may explain inconsistencies in the literature regarding whether physiologic or dietary factors contribute to obesity.

GENETIC SIGNATURES FOR INSULIN-ASSOCIATED PHENOTYPES

With the advent of high throughput genetic analysis, it has become possible to identify suites of single nucleotide polymorphisms (SNPs) that associate with insulin phenotypes. One recent study tested the hypothesis that genes conferring relatively greater insulin secretion would be related to obesity, on a cross-sectional basis. The study was conducted as a Mendelian association study [17▪▪], where preselected SNPs associated with insulin secretion were used as independent variables in statistical models predicting BMI. Three SNPs were closely associated with insulin-30; these SNPs were close to the genes *HHEX*, *QPCTL*, and *CDKAL1*, all of which have been associated with obesity or type 2 diabetes. Results indicated that higher genetically determined insulin secretion was associated with higher BMI. In contrast, SNPs for higher BMI were not associated with insulin-30. These results suggest that genetic testing could be used to assess risk for obesity.

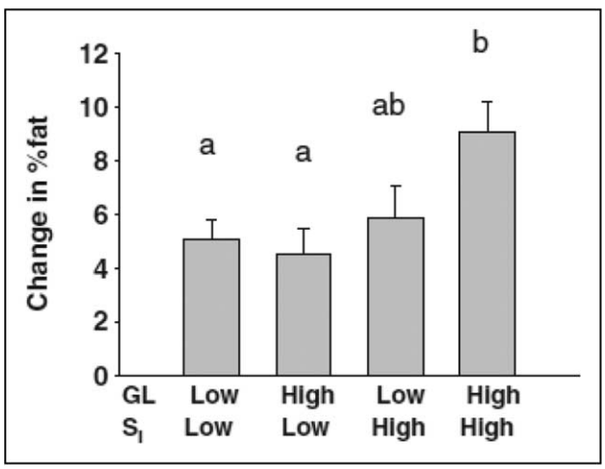

FIGURE 4. Among formerly obese, weight reduced African-American women, those who were relatively insulin sensitive (high S_I) and consumed a free-living diet relatively high in glycemic load gained the most fat over 1 year [8]. Reproduced with permission from Figure 3a of [8].

In a second study, genetic determinants of insulin resistance were probed in a sample of up to 188,577 individuals [18▪▪]. Fifty-three loci associated with insulin resistance and were used to derive a '53-SNP' genetic score. This score was associated with greater risk for type 2 diabetes and coronary heart disease, and with lower body fat percentage, BMI, and hip circumference (Fig. 5a). In a sub-sample with Dual-energy X-ray absorptiometry (DXA) data, the 53-SNP score was associated with lower body fat in the leg and gynoid regions (Fig. 5b). Individuals in the highest quintile had an average of 712 g less leg fat mass than individuals in the bottom quintile. Quantitative Trait Locus analysis for putative effector genes revealed three genes, *L3MBTL3*, *DNAH10*, and *CCDC92*, implicated in lipid storage. As such, the results point to a primary effect of genetic predisposition on impaired adipose function, which in turn precipitates insulin resistance. Thus, insulin resistance *per se* may not promote leanness; rather, both insulin resistance and leanness are consequences of genetically determined defects in adipocyte differentiation.

A final study, 'DIETFITS', was conducted to test the main effect of diet composition (low fat versus low carbohydrate) on weight loss, and interactive

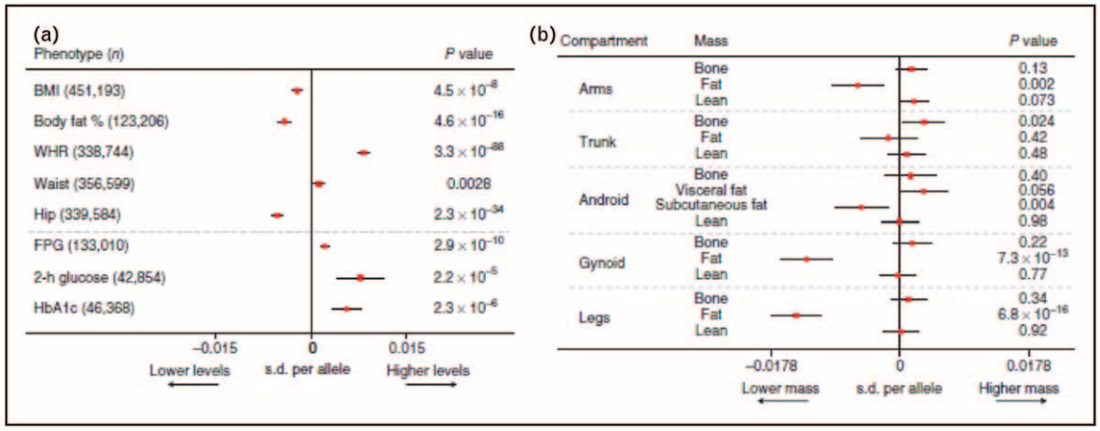

FIGURE 5. Association of genetic insulin resistance with measures of obesity (a) and body fat distribution (b) [18▪▪].

effects with genotype (*PPARG*, *ADRB2*, *FABP2*) or insulin-30 [19]. Results indicated no main effect of diet on body weight, and no interactive effect with genotype or insulin-30. Although widely perceived as failing to support a personalized medicine approach to obesity treatment, this conclusion may be premature. Our data have shown that, in the context of negative energy balance, differences between diets are manifest in body composition but not 'weight'; that is, those on a low glycemic (versus low-fat) diet lost more body fat but preserved lean mass [20]. Further, the mandated energy restriction may have masked the potential effect of diet composition on adherence [21] and voluntary intake. In addition, both diets were low in added sugar and refined grains, precisely the diet components responsible for the obesogenic effect of high-carbohydrate diets, particularly among individuals with an insulin-driven phenotype. The study has extensive genetic analyses and insulin sensitivity data, as well as body composition by DXA on a sub-sample. It is possible that further analyses will yield additional results.

IT'S NOT JUST ABOUT 'WEIGHT': ENERGY PARTITIONING

Although the goal of 'weight loss' is ideally 'fat loss', energy-restricted diets are generally associated with simultaneous loss of lean mass. Intriguingly, carbohydrate-restricted diets are reported to preserve lean mass [22–26]. In cases of carbohydrate intake less than 50 g/d (i.e., ketosis), this effect may be attributed to a decrease in gluconeogenesis and accompanying amino acid efflux from muscle. However, low glycemic diets likewise result in loss of more total body fat (but not more lean mass) when compared to low-fat diets, despite no difference in 'weight' loss (Fig. 6) [20]. In a cross-over study of women with polycystic ovary syndrome, 8 weeks of a low glycemic versus low-fat diet prescribed at a eucaloric level resulted in significantly greater loss of total fat. In addition, the low glycemic diet produced decreases in visceral, abdominal subcutaneous, and intermuscular adipose tissue, whereas the low-fat diet resulted in loss of lean mass [22]. Again, weight loss was minimal and not different between arms. These observations suggest that diet composition-mediated changes in energy partitioning occur independent of weight change. Whether these changes occur to a greater extent in individuals with specific metabolic phenotypes has not been investigated.

IT IS NOT JUST ABOUT 'WEIGHT': METABOLIC HEALTH

Weight loss is also intended to improve metabolic health. Thus, diet effects on disease risk factors that are independent of weight loss should be examined. In DIETFITS, lower triglycerides were observed in the low-carbohydrate group, and lower LDL

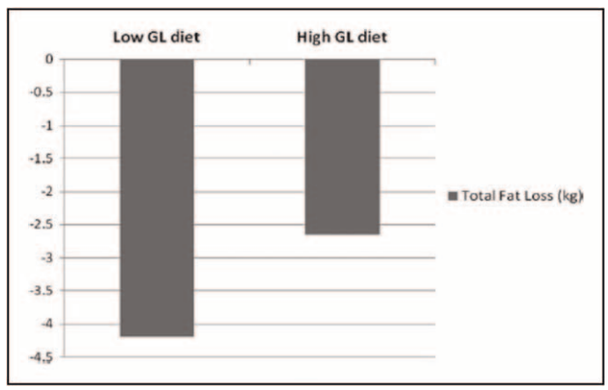

FIGURE 6. Greater loss of body fat on hypocaloric low glycemic load versus high glycemic load diet despite no different in weight loss [20].

cholestrol was observed in the lower fat group. In a large randomized clinical trial, a significantly greater decrease in blood pressure was observed with a carbohydrate-restricted than a fat-restricted diet, despite similar weight loss [27]. In patients with type 2 diabetes, metabolic health (A1c, fasting glucose, systolic blood pressure) was clearly improved to a greater extent with carbohydrate restriction than fat restriction [28], despite identical and significant weight loss. The net effect of diet composition on disease risk factors may depend on the metabolic health of the patient or population, with a carbohydrate-restricted diet being particularly beneficial among patients with type 2 diabetes.

WEIGHT LOSS MAINTENANCE

It has been said that any diet is effective for weight loss if it is maintained [29]. However, weight loss maintenance has remained elusive. The seemingly inevitable weight regain has been attributed in part to intractable hunger. Even 1 year following weight loss, hunger remains elevated, along with a hormone profile compatible with increased hunger [30]. In addition, energy expenditure may be dramatically lower than predicted based on body size [31], and the efficiency of physical movement may be higher than predicted [32] up to 6 years after weight loss.

The possibility that diets of a given macronutrient composition could modulate these physiological compensatory mechanisms has not been widely addressed. However, patients who show elevations in serum ketones seem immune from elevated hunger following weight loss [33]. This observation is compatible with lower voluntary food intake yet similar reported satiety in patients consuming a ketogenic (very low carbohydrate) than a control diet [28,34]. In a cross-over study following weight loss (during weight maintenance), patients had higher energy expenditure when carbohydrate-restricted than when fat-restricted, an effect that appeared to be carbohydrate dose-dependent [35]. In a recent very-low-calorie weight loss study, consumption of a ketogenic diet prevented the expected decrease in energy expenditure following weight loss, and preserved lean mass [36]. Although the mechanistic basis for an effect of carbohydrate restriction on energy expenditure is not clear, higher glucagon [37,38], and perhaps higher uncoupling protein due to lower insulin [39], may contribute.

Several studies have yielded provocative results suggesting that metabolic phenotype may interact with diet composition to predict success with weight loss maintenance. Most recently, a re-analysis of the DiOGenes data revealed that among a subgroup of weight-reduced patients with impaired fasting glucose, an ad-libitum high glycemic diet resulted in 4.49 kg weight re-gain over 26 weeks, whereas an ad-libitum low glycemic diet resulted in a further weight loss of 1.34 kg (a between-diet differential of 5.83 kg) [40▪▪]. As with the study shown in Fig. 2, the results from DiOGenes suggest that the body weight set-point in these patients was re-set to a new, lower, level when the individuals consumed the low glycemic diet. Among patients with normal fasting glucose, the diet effect was qualitatively similar but smaller in magnitude (a differential of 1.44 kg). Although fasting insulin was significantly higher in the group with impaired fasting glucose, postchallenge insulin was not examined. In a second study, patients with high baseline insulin-30 were more sensitive both to the hypometabolic effect of weight loss, and to the modifying effect of diet during subsequent weight maintenance, such that the reduction in energy expenditure with weight loss was mitigated to a greater extent with a low carbohydrate versus a low-fat diet [25]. These results suggest that weight loss may be easier to maintain with the low-carbohydrate diet. Finally, among participants with high fasting insulin, adherence to a carbohydrate-restricted diet was higher than adherence to a fat-restricted diet [21]. Taken together, these observations suggest that transitioning patients to a carbohydrate-restricted diet following weight loss may induce physiologic changes that help maintain weight loss, particularly among patients with specific metabolic phenotypes.

CONCLUSION

A carbohydrate-restricted diet may allow patients with high insulin secretion to defend a new, lower, body fat set-point without experiencing hunger, and without intentional energy restriction. Research is needed to clarify the genotypic and phenotypic markers that may be used in identifying these patients, and developing an algorithm for a personalized treatment approach. Research is needed to determine whether carbohydrate-restricted diets can promote weight loss maintenance among individuals with high insulin secretion by preventing or minimizing the compensatory changes in hunger and energy expenditure that occur with weight loss. Mechanistic studies examining hunger/satiety hormones, uncoupling proteins, and other variables contributing to energy balance are needed in studies involving diet composition and weight loss maintenance.

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Conflicts of interest

There are no conflicts of interest to disclose.

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- ■ of special interest
- ■■ of outstanding interest

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