A Shift Towards a High-Fat Diet in the Current Metabolic Paradigm: A New Perspective

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Title: *A Shift Towards a High-Fat Diet in the Current Metabolic Paradigm: A New Perspective*

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**Abstract**

Investigations into the relationship between dietary carbohydrate restriction and health are mixed. Current guidelines for nutrition promote low-fat foods and higher carbohydrate consumption for optimal health and weight loss. However, high fat, lower carbohydrate diets are revealing both intra and extracellular adaptations which have been shown to elicit favorable cardio-metabolic changes associated with obesity. Moreover, dietary fat is associated with higher satiety levels from hormones adiponectin, leptin, and cholecystokinin. In addition, insulin responses from high glycemic carbohydrates are known to alter these pathways potentially leading to an increase in energy consumption and a possible mechanism for obesity. There is convincing evidence of beneficial effects of controlled trials implementing high fat, low carbohydrate diets in both sedentary and obese individuals, but longer duration clinical trials are required to confirm this hypothesis.

**Key Words:** Carbohydrate restriction; Hormone; Obesity; Dietary fat; Mitochondria; Hypothalamus
Introduction

In a scientific statement provided by the American Heart Association Nutrition Committee, excess energy consumption, particularly in the form of dietary fats, is associated with metabolic dysfunction, obesity, and type 2 diabetes mellitus. Current recommendations include low-fat dairy, lean meats, high fiber whole grain foods, and substantial fruits and vegetables [1]. According to the Centers for Disease Control and Prevention, obesity affects 37% of adults and is a leading cause of preventable deaths [2]. Furthermore, a suggested intervention for combating weight gain in the U.S. is dietary manipulation and caloric reduction. Although dietary fat (9 kcal g\(^{-1}\)) is twice the energy density of either protein (4 kcal g\(^{-1}\)) or carbohydrates (CHO) (4 kcal g\(^{-1}\)), high fat, low CHO (HFLC) diets are showing potentially beneficial effects in relation to weight loss and metabolic health markers in the scientific literature [3-5]. At a glance, the HFLC diet is merely another method for decreasing overall caloric intake, however, recent literature is emerging, suggesting that higher ingestion of dietary fats (coupled with lower CHO) might elicit beneficial alterations in hormonal, enzymatic, and mitochondrial expression.

Pathophysiologic mechanisms of a HFLC diet

Although it is beyond the scope of this article to sufficiently detail the intricate process of bioenergetics, a general overview is provided to add context to the following discussion. The mammalian endogenous system is concerned with both the preservation and conversion of energy within a living cell. This energy is known as adenosine triphosphate (ATP) and is fueled by the breakdown of three macronutrients: proteins, fats, and CHO. Although the relative
contribution of each depend on current stimuli from both dependent and independent oxidative pathways, a lack of one macronutrient will result in enhanced oxidation and utilization of the two other macronutrients for ATP production in attempt to maintain homeostasis.

Current research shows that when CHO are reduced and dietary fat increased, an individual’s fat oxidation will rise to balance fat ingestion [6, 7]. Subsequently, due to the increase in fat oxidation, several adaptations may occur at the hormonal level with a chronic HFLC diet, possibly aiding weight loss.

The hypothalamus is a region of the brain that regulates hunger through a series of hormones and neurotransmitters. The neuron Neuropeptide Y (NPY) is of primary importance in either upregulating or downregulating satiety, the feeling of fullness. During exogenous fat ingestion, receptors lining both the mouth and duodenum signal for the release of cholecystokinin (CCK) which then communicates to NPY to slow digestion of the small intestine so fats may be adequately digested [8]. Secretion of CCK further augments satiety by stimulating downstream digestion and signaling for the release of adipocytokines; leptin and adiponectin.

Leptin is a major regulator of energy homeostasis. While in a fed state, leptin alters NPY receptors to inhibit its production and depolarize the neuropeptide receptors [9]. Adiponectin amplifies the effects of leptin by further downregulating the hypothalamic expression of NPY via corticotropin-releasing hormone (CRH) pathway [10]. The CRH pathway is thought to be a primary activator of the hypothalamus when extra and intracellular stores are decreased.

The aforementioned hormones are important in understanding the affects of macronutrient composition on satiety. The consumption of lower glycemic index foods, such as proteins and dietary fats, as well as the reduction of dietary CHO, typically results in greater
satiation as well as improved body composition and blood lipid profiles [11-13]. Layman and his team found that overweight women who consumed a diet with reduced dietary CHO was more effective than a high CHO diet in maintaining lean mass (0.88 kg vs 1.21 kg), reducing body fat (5.60 kg vs 4.74 kg), and providing a higher satiety rating, respectively [14].

However, chronic hyperinsulinemia and defective pancreatic beta cells have been shown to decrease efficiency in weight management and indirectly lead to resistance in the preceding pathways [15]. While also a storage hormone involved in glucose metabolism, insulin is capable of acting directly on the hypothalamus to increase satiety [16]. However, a previous study found that subjects who consumed meals with high glycemic foods also had an inverse relationship between the gut hormone glucagon-like peptide 1 (GLP-1) and insulin [17]. GLP-1 is an intestinal hormone that functions as a stimulus for insulin secretion and inhibitor of gastric emptying and to a lesser extent, NPY. A diminished response in GLP-1 would also result in an attenuated satiation and when coupled with the reactive hypoglycemia from a high glycemic meal, could be a potent appetite stimulant within the hypothalamus. Furthermore, excess glucose from high glycemic meals not immediately utilized, are then converted to palmitic acid and have been shown to potentially decrease leptin sensitivity [18, 19]. These suggested mechanisms have been concluded in several studies to be a potential indicator for overconsumption of caloric energy, ultimately leading to obesity [20-23].

Finally, HFLC diets can decrease circulating insulin, improve glucose uptake efficiency, and eventually, increase insulin sensitivity [24-27]. While the investigators acknowledge the multiple physiological roles that insulin plays in maintaining homeostasis both peripheral and central, it is worth noting that excess production and secretion of insulin, from overconsumption
of both caloric energy and high glycemic CHO, cannot be ignored in the current obesity epidemic.

**AMPK: Enhancing the mitochondria**

AMP-activated protein kinase (AMPK) is a cellular energy sensor capable of detecting shifts in the AMP:ATP ratio and phosphorylating downstream compounds to maintain energy equilibrium. During periods of exercise or caloric restriction, AMPK activates a host of metabolic cascades shown to inhibit insulin secretion, glycogen and fatty acid synthesis, and increase glucose oxidation, and fatty acid utilization [28-31]. To the investigators knowledge, few studies have compared the affects of a diets macronutrient composition on AMPK expression and activity in humans.

Draznin et al. randomized obese subjects either to a HFLC diet (50% fat, 30% CHO, 20% protein) or high CHO, low fat (HCLF) diet (20% fat, 60% CHO, 20% protein). Both diet groups were calorically restricted by 30% below baseline. After 5-days, both the HFLC and HCLF group had modest weight loss, however, only the HFLC group showed significant AMPK phosphorylation. In a follow up study, Draznin et al. showed significant alterations in AMPK resulting from a 5-day, hypercaloric (40% above baseline) HFLC diet in healthy males and females [32]. The researchers concluded that restricted CHO availability is a potent stimulus for AMPK phosphorylation.

Additionally, HFLC diets have potential to promote mitochondrial adaptations, similar to endurance exercise, mediated via the AMPK pathway in both lean and obese subjects.

Bergouignan et al. showed an increase in silent mating type information regulation 2 homolog 1
(SIRT1), de-acetylated peroxisome proliferator-activated receptor γ coactivator-1-α (PGC1-α), and AMPK during a short-term high fat diet using healthy and overweight individuals [33]. These acute molecular adaptations are in agreement with previous studies of longer durations which have attributed such changes to an increase in oxidative capacity by up-regulating mitochondrial biogenesis [34, 35]. Increasing mitochondrial efficiency and function has two primary benefits for overweight and sedentary individuals: increased fatty acid oxidation and an improved cellular redox environment [34, 36, 37]. Both of which have direct implications for individuals suffering from chronic cardio-metabolic dysfunction (i.e., CVD, atherosclerosis, insulin resistance).

Obesity is defined as a nutritional disorder, identified as excessive adipose accumulation [38] and is strongly correlated with type 2 diabetes mellitus. Both populations consistently show an increase in plasma free fatty acid concentrations, generally associated with impaired carnitine acyltransferase 1 transporters within the mitochondria [39]. Obese individuals have also been linked to chronic oxidative stress which can further contribute to insulin resistance and several other adverse cardio-metabolic issues and subsequently, impaired mitochondrial function [38]. Therefore, it would seem appropriate to combat a nutritional disorder with a diet intervention, such as a HFLC diet, which has shown identical metabolic alterations to that of physical training and consequently, leading to a reduction in body mass, improved cellular signaling, and efficient hormonal regulation.

Conclusion

In conclusion, the macronutrient profile of a diet, not just caloric load, does matter for health and weight loss. It should be noted, however, that dietary manipulation is only a part of
solving the obesity epidemic. While the current article is a hypothetical perspective regarding diet, the investigators agree with present research, concrete in its findings, that physical activity positively alters the aforementioned pathways. Therefore, although scientists still debate the composition of a diet, exercise should always be promoted when the topics include health and weight-loss. Future research should consider longer HFLC diet durations with a directed focus on the responses of signaling proteins or metabolites that may play a central role in cellular adaptations that can affect cardio-metabolic health.
References


Research Highlights:

- A mechanistic pathway of carbohydrate restriction and obesity is outlined.
- NPY, CCK, and CRH rely on dietary fat and cellular signaling for improving health.
- AMPK has shown to respond favorably to dietary fat but not to carbohydrates.
- The pathways explain a potential dietary intervention in combating obesity.