Nutrition Targeting by Food Timing: Time-Related Dietary Approaches to Combat Obesity and Metabolic Syndrome[1–4]

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ABSTRACT

Effective nutritional guidelines for reducing abdominal obesity and metabolic syndrome are urgently needed. Over the years, many different dietary regimens have been studied as possible treatment alternatives. The efficacy of low-calorie diets, diets with different proportions of fat, protein, and carbohydrates, traditional healthy eating patterns, and evidence-based dietary approaches were evaluated. Reviewing literature published in the last 5 y reveals that these diets may improve risk factors associated with obesity and metabolic syndrome. However, each diet has limitations ranging from high dropout rates to maintenance difficulties. In addition, most of these dietary regimens have the ability to attenuate some, but not all, of the components involved in this complicated multifactorial condition. Recently, interest has arisen in the time of day foods are consumed (food timing). Studies have examined the implications of eating at the right or wrong time, restricting eating hours, time allocation for meals, and timing of macronutrient consumption during the day. In this paper we review new insights into well-known dietary therapies as well as innovative time-associated dietary approaches for treating obesity and metabolic syndrome. We discuss results from systematic meta-analyses, clinical interventions, and animal models. *Adv Nutr* 2015;6:214–223.

Keywords: obesity, metabolic syndrome, food timing, abdominal obesity, hunger and satiety, diabetes melitus, cardiovascular diseases, leptin, ghrelin, adiponectin

Introduction

Severe obesity is often accompanied by unremitting hunger without sensations of satiety, which leads to chronic overeating and enhanced visceral adipose tissue accumulation. In this scenario, losing weight is almost impossible and development of metabolic syndrome is accelerated. Metabolic syndrome is a cluster of symptoms including abdominal obesity, hypertension, elevated fasting plasma glucose, dyslipidemia, and an enhanced inflammatory state. Under these conditions, the probability of developing diabetes mellitus and cardiovascular disease is high. Because obesity and metabolic syndrome are associated with diminished quality of life and increased mortality rates, countless treatments have been developed to reduce their prevalence. A considerable amount of research has been dedicated to evaluating the efficiency and safety of these treatments in an attempt to establish evidence-based recommendations.

Currently, when dealing with obese subjects with metabolic syndrome, the interventions of choice include bariatric surgery, medication for weight reduction, medication for the comorbidities associated with metabolic syndrome (diabetes, hyperlipidemia, and hypertension), or diet. Both bariatric surgery and medications present certain side effects and risks; therefore, dietary modifications that are able to induce sustained weight reduction and long-term attenuation of metabolic pathogenesis should be considered the first line of treatment. Yet, most obese subjects who are trapped in the vicious cycle of obesity fail to maintain any kind of long-term diet regimen and eventually regain body weight (1–3). Investigations focused on long-term successful weight loss maintenance such as the National Weight Control Registry (4–6) have yet to produce definitive recommendations. Nevertheless, long-term prospective studies have the potential to provide meaningful solutions in the future. A notable amount

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of information documents the efficacy of balanced, low-calorie, and very low–calorie diets. Scientists and dietitians have also investigated the outcomes of modifying the macronutrient composition of these diets. However, comparisons of weight-loss diets with varying proportions of fat, protein, and carbohydrates have demonstrated no meaningful differences in percentage of weight loss, waist circumference reduction, hunger and satiety, adherence levels, and weight regain (7). Unequivocal conclusions have been elusive regarding the advantages of any of these diets to ameliorate risk factors for diabetes and cardiovascular disease (8–11).

In searching for nutritional guidance for obese patients with metabolic syndrome, traditional diets were also analyzed. The most studied is the Mediterranean diet. Evidence-based diets such as Dietary Approaches to Stop Hypertension (DASH) have also been widely studied. These dietary regimens will be discussed herein.

Evidence from animal models has demonstrated that feeding at the "wrong time" can lead to obesity. Mice fed a high-fat diet during the light cycle (usual sleeping time) gained more weight than controls, despite similar food intake and estimated energy expenditure (12). Additional studies in animals have shown that restricting feeding times can prevent diet-induced obesity and improve metabolic markers (13, 14). The most recent studies in human subjects report that the timing of meals during daylight hours has critical implications in the prevention of obesity, weight loss and regain, appetite, insulin resistance, and metabolic syndrome (15, 16). Consumption of specific nutrients with defined distribution times during the day influence these variables as well (16, 17).

The religious fast of Ramadan maintained by devout Muslims over a month-long period every year provides a unique time-related dietary model. This ancient tradition is characterized by fasting during daylight hours with food consumption predominantly concentrated on a high-calorie, high-carbohydrate evening meal. Numerous clinical studies have examined Ramadan's impact on body weight and metabolic health. A recent meta-analysis (18) reported that Ramadan's beneficial effects on metabolic status included lowered blood glucose concentrations, improved lipid profiles, and reduced body weight. However, these results were gender-related.

Recently, we studied the effect of a low-calorie diet with carbohydrates eaten only at dinner as a possible time-related dietary solution for abdominal obesity and metabolic syndrome (19, 20). We present our conclusions in the following pages.

In this review, we summarize recent research findings for both long-standing diets and novel, time-related dietary regimens whose goals are to combat the vicious cycle of abdominal obesity and metabolic syndrome. The paper discusses results from current comprehensive meta-analyses on long-standing well-studied diets. New dietary approaches are presented along with the latest randomized, controlled trials and animal studies from research laboratories around the world and findings from our own research projects. The paper focuses on time-related dietary approaches and their efficacy in ameliorating abdominal obesity and its comorbidities.

Current State of the Knowledge

Are calories the whole story?

Data from clinical studies indicate that long-term caloric restriction with adequate intake of nutrients reduces the risk of developing type 2 diabetes, hypertension, and cardiovascular disease (21). The effectiveness of simple low-calorie diets was evaluated in a randomized, controlled dietary intervention conducted by Papadaki et al. in 2013 (22). Changes in obesity measures among 938 overweight and obese adults from 8 European cities assigned a low-calorie diet for 8 wk were studied. It was found that the low-calorie diet induced favorable changes in all outcomes, including over 10% reduction in body weight and body fat percentage. These outcomes were similar to numerous other studies that report weight reduction by consumption of low-calorie diets. It remains to be determined whether low-calorie diets can substantially attenuate metabolic risk factors. A retrospective study conducted by Paull-Forney et al. (23) in 2014 reviewed participants' charts with the goal of assessing the effect of a low-calorie diet program that included behavioral intervention on markers of metabolic syndrome. During $\geq$12 wk in a community-based medical weight-loss program, 445 participants were required to attend weekly behavioral education sessions and were encouraged to participate in daily physical activity. Sixty eight percent of participants, completing 12 wk of the program, achieved >10% initial body weight loss as expected. After the intervention, the number of participants meeting one of the criteria for metabolic syndrome (i.e., high waist circumference, TGs, fasting plasma glucose, and blood pressure) or for overall metabolic syndrome was reduced. Use of hypoglycemic and antihypertensive medications was also decreased.

It appears that, overall, low-calorie diets are an efficacious strategy for weight loss and can offset metabolic syndrome. The real challenges of this type of regimen are the high dropout rate and difficulty in maintaining achievements over time. A large observational cohort study conducted in Sweden by Hemmingsson et al. (24) in 2012 quantified weight loss and dropout rates during a commercial weight-loss program. Weight loss was induced with a very-low–calorie diet (500 kcal/d, n = 3773), low-calorie diet (1200–1500 kcal/d, n = 4588), or restricted diet (1500–1800 kcal/d, n = 676). After 1 y, subjects consuming the very low–calorie diet lost >11 kg with a dropout rate of 18%; subjects consuming the low-calorie diet lost almost 7 kg with 23% dropout; and the restricted diet participants lost nearly 5 kg during which 26% of them dropped out. It was easy to define a linear dose–response relation between energy intake and reduced body weight, waist circumference, and percentage body weight. Dropout rates were lowest in the very-low–calorie diet group, followed by the low-calorie diet group, and finally the restricted diet group, presenting an approximately linear correlation.

Additional studies show that in people who completed a short (2 mo) or long (1 y) dietary protocol of any kind and achieved final body weights lower than initial levels,

the main challenge was maintenance, which clearly represents the major difficulty in obesity treatment. It was found that treatment with a very-low–calorie diet (800 kcal/d) or low-calorie diet (1200 kcal/d) was associated with substantial initial weight loss, but also greater weight regain compared with weight loss achieved through a more moderate restriction (25). Maintaining substantial weight loss requires strategies such as specific dietary interventions, exercise, behavioral treatments, or antiobesity drugs. In 2014, a systematic review and meta-analysis was conducted by Johansson et al. (25) to quantify the effects of these methods on weight-loss maintenance after a low- or very-low–calorie diet. Twenty randomized, controlled trials were included with 3017 participants who originally followed a low- or very-low–calorie diet and thereafter were randomly assigned to either a maintenance strategy, control, or placebo. As expected, during the initial diet period, the pooled mean weight change was >12 kg. Antiobesity drugs improved weight-loss maintenance by 3.5 kg, meal replacements by 3.9 kg, and high-protein diets by 1.5 kg. Exercise and dietary supplements did not substantially improve weight-loss maintenance compared with controls.

Does changing macronutrient proportions make a difference?

There is no question that low-calorie diets facilitate weight loss and attenuate metabolic risk factors. Yet, it is still not clear if they can be maintained for long periods or if health improvements are enduring. Over the years, the various macronutrient proportions of weight-loss diets have been tested and evaluations have been made on whether focusing on fat, carbohydrates, or protein is superior for weight loss, weight maintenance, hunger and satiety, and metabolic health. In 2009, Sacks et al. (7) compared diets that differed in their macronutrient proportions. Diets that emphasized protein, fat, or carbohydrate consumption demonstrated similar results. The intervention included 811 overweight adults who were randomly assigned to 1 of 4 diets. The diets consisted of similar foods and met guidelines for cardiovascular health, and participants were offered group and individual instructional sessions for 2 y. At 6 mo, participants in all diet groups had lost a mean of 7% of their initial weight; however, they began to regain weight after 12 mo. At 2 y, maintenance of weight loss was similar among participants regardless of the proportions of protein, fat, and carbohydrates in their diets. Hunger and satiety, satisfaction with the diet, and attendance at group sessions were similar for all groups. The percentage of participants with metabolic syndrome decreased after 2 y but, again, no difference was observed among groups.

A second randomized trial conducted by de Souza et al. (26) in 2012 was designed to determine whether energy-reduced diets that emphasized fat, protein, or carbohydrates differentially reduced total, visceral, or hepatic fat or preserved lean mass. Participants were randomly assigned to 4 weight loss diets. Changes from baseline were compared between assigned amounts of protein (25% or 15%) and fat (40% or 20%), and across 4 carbohydrate concentrations (35–65%). At 6 mo, participants lost 3.5% of their lean mass and 12.4% body fat (13.8% abdominal fat, 13.6% subcutaneous fat, and 16.1% visceral fat) compared with baseline values, with no differences between diets. Hepatic fat was also reduced, with no differences among groups. Participants regained 40% of these losses after 2 y, again with no differences among dietary treatments.

Over the years, each macronutrient has been scrutinized regarding its role in the development of obesity and metabolic syndrome. The first macronutrient that was "accused" of causing the "epidemic of the millennium" was fat. This led to a global trend toward low-fat diets. With our current understanding of metabolism and endocrinology, we can look back and see that this approach was both misguided and oversimplified. A large meta-analysis published in 2014 by Schwingshackl and Hoffmann (27) confirmed that high-fat diets actually improve lipid profiles, glycemic control, and blood pressure.

In the days when low-fat diets were considered the solution for overcoming obesity and its comorbidities, high-carbohydrate diets, often with high–glycemic index foods, were popular. With the understanding that fat is not always the macronutrient to blame and that large proportions of carbohydrates are not always appropriate, a new debate around the efficacy and safety of low-carbohydrate and high-protein diets entered the spotlight. Recent comprehensive meta-analyses conducted in 2013 and 2014 found that low-carbohydrate diets not only decreased body weight, but also increased fat loss and reduced fasting TGs and insulin (28, 29), glycosylated hemoglobin A1c, and blood pressure (30), with overall improvement of cardiovascular disease risk factors (31).

Is it possible that the answer is hidden in traditional diets? The Mediterranean diet

While looking for a solution to the obesity and metabolic syndrome epidemics, much attention has been given to well-known traditional diets. The most studied among these diets is the Mediterranean dietary pattern common in Greece, southern Italy, and Spain. The Mediterranean diet is characterized by the daily consumption of olive oil, vegetables, fruits, nuts, whole grains, and legumes; small amounts of dairy products, fish, and poultry; moderate consumption of alcohol; and a relatively low consumption of red meat. Several large studies, reviews, and meta-analyses that summarize the current knowledge of the Mediterranean diet have been published.

In 2011, Esposito et al. (32) evaluated the effect of the Mediterranean diet on body weight in a meta-analysis of 60 randomized, controlled trials with a total of 3436 participants. They reported that following a Mediterranean dietary pattern can reduce body weight and BMI. Associations were strengthened when energy restriction, increased physical activity, and length of study were included in the analysis.

A second meta-analysis of epidemiologic studies and randomized, controlled trials published in 2011 by the same

group of researchers assessed the effect of the Mediterranean diet on metabolic syndrome and its components (33). The study included 35 clinical, 2 prospective, and 13 cross-sectional studies, with 534,906 participants. The combined effect showed that adherence to the Mediterranean diet was associated with a reduced prevalence of metabolic syndrome and its risk factors, including high waist circumference, TGs, glucose, and blood pressure. These conclusions were strengthened by an updated systematic review, which focused exclusively on the effect of the Mediterranean diet on metabolic syndrome. The review included epidemiologic observational studies and clinical trials through 2013 (34). The new evidence further supported the beneficial role of adherence to the Mediterranean diet in reducing the prevalence and progression of metabolic syndrome.

The most recent meta-analysis of prospective studies, published in 2014 by Koloverou et al. (35), evaluated the effect of the Mediterranean diet on the development of type 2 diabetes. Seventeen studies (1 clinical, 9 prospective, and 7 cross-sectional) were identified, with 136,846 participants. It was found that a high adherence rate to the Mediterranean diet was associated with a 23% reduced risk of developing type 2 diabetes.

Finally, a very large study conducted by Sofi et al. (36) in 2013 examined the association between the Mediterranean diet and overall health status. All available prospective cohort studies investigating adherence to the Mediterranean diet and health outcomes were included. The collective population reached 4,172,412 subjects. Findings show that a 2-point increase in adherence score to the Mediterranean diet led to a 10% reduced risk of cardiovascular disease and an 8% reduction in overall mortality.

Shall we go with evidence-based diets? DASH

DASH is a dietary pattern promoted by the National Heart, Lung, and Blood Institute in the United States to prevent and control hypertension. DASH emphasizes consumption of vegetables, fruits, whole grains, legumes, nuts, fish, and poultry, with limitations on sugar-sweetened foods and beverages, added fats, and red meat. DASH is based on NIH studies that examined 3 dietary plans and their results. DASH reduced blood pressure in patients with prehypertension and hypertension with no changes in body weight. In addition, it is considered to be a well-balanced dietary pattern for the general public (37, 38).

A systematic review and meta-analysis of all randomized clinical trials, which evaluated the effect of DASH on blood pressure, was published by Parvane Saneei et al. (39) in 2014. Seventeen randomized, controlled trails with 2561 participants were included. Data showed that DASH significantly reduced both systolic and diastolic blood pressure. A greater decrease in blood pressure was observed in studies that included energy restriction and in which subjects were hypertensive at baseline.

In 2013, Salehi-Abargouei et al. (40) summarized and quantified the longitudinal effects of DASH on the incidence of cardiovascular diseases. Cohort studies that examined DASH in relation to coronary heart disease, stroke, or heart failure were selected. Exclusion criteria were individuals with known cardiovascular disease risk factors such as diabetes mellitus, metabolic syndrome, obesity, or hypertension. Results strongly supported the fact that following a DASH dietary pattern significantly reduced risk of cardiovascular disease, coronary heart disease, stroke, and heart failure. In an additional systematic review and meta-analysis by the same authors, the effects of DASH on managing the risk factors of type 2 diabetes were investigated (41). Data showed that following DASH significantly reduced fasting insulin concentrations with little beneficial effect on fasting blood glucose and HOMA-IR.

Time-related dietary approaches: time to eat, meal timing, and time of specific macronutrient consumption

The search continues for groundbreaking, easy-to-implement dietary regimens for obese patients with metabolic disease. Recent studies have investigated the interactions between timing of food consumption, weight regulation, and metabolic status. Studies in animal models and clinical studies have shown that timing of overall food consumption, meal times, and distribution of specific macronutrients over the course of the day can substantially affect anthropometric and metabolic variables. This indicates that new therapeutic strategies should take into consideration not only caloric intake, macronutrient proportion, or healthy food groups, but also when it is preferred to eat, i.e., food timing.

Time to eat. An animal study performed by Arble et al. (12) in 2009 reported that nocturnal mice fed a high-fat diet solely during the light phase gained significantly more weight than mice fed the same amount of food during the dark phase. In another animal study conducted by Hatori et al. (14) in 2012, mice were subjected to either ad libitum or time-restricted feeding (8 h/d) of a standard or high-fat diet for >100 d. It was shown that, despite consumption of equivalent amounts of energy, mice under time-restricted feeding were protected from the adverse effects of the high-fat diet (obesity, hyperinsulinemia, hepatic steatosis, and inflammation). The authors concluded that a time-restricted feeding regimen is a nonpharmacologic strategy against obesity and associated diseases. Similar animal studies performed by Sherman et al. (13) in 2012 tested whether 18 wk of restricted feeding could attenuate the disruptive effects of diet-induced obesity. Mice fed a time-restricted high-fat diet consumed the same amount of calories as mice that consumed a low-fat diet ad libitum. However, the time restriction led to a 12% reduction in body weight, 21% reduced cholesterol concentrations, and 1.4-fold improved insulin sensitivity. Compared with the mice that consumed a high-fat diet ad libitum, the timed high-fat diet led to 18% lower body weight, 30% decreased cholesterol concentrations, 10% reduced TNF-α concentrations, and 3.7-fold improved insulin sensitivity. Mice fed the timed high-fat diet appeared better satiated and had 25% lower ghrelin concentrations than the mice fed the timed

low-fat diet. These findings suggest that food timing can prevent obesity and rectify the possible harmful effects of a high-fat diet.

Timing of meals. In 2011, Wu et al. (42) tested the absence of breakfast or supper on body weight and adiposity in a rodent model. Rats were divided into 3 groups, including controls, a no-first-meal group, or a no-last-meal group. All rats were fed the same amount of food daily; however, rats from the no-last-meal group demonstrated lower body-weight gain and adipose tissue accumulation.

A prospective longitudinal study conducted by Garaulet et al. (43) in 2013 in 420 overweight and obese Spanish participants evaluated the role of main-meal timing on the effectiveness of the weight-loss process and long-term maintenance. Subjects voluntarily participated in a 20 wk diet and behavioral treatment based on the Mediterranean eating pattern. Patients received recommendations on the number of portions they should eat from each food group with no advice regarding food timing or distribution of daily energy intake during the treatment. It was shown that those who ate lunch later in the day (main meal in Mediterranean populations) lost significantly less weight than those who ate lunch early, despite similar energy intake and expenditure, dietary consumption, macronutrient distribution, sleep duration, and hormone levels.

Another randomized, open-label, parallel-arm study performed by Jakubowicz et al. (15) in 2013 examined the association between time of nutrient intake during the day and metabolic syndrome. For 12 wk, 93 overweight and obese women with metabolic syndrome switched between a high-calorie breakfast and a high-calorie dinner, with an overall similar daily caloric intake. The large breakfast group showed greater weight loss and waist circumference reduction. Overall, daily ghrelin and mean hunger scores were significantly lower, whereas mean satiety scores were significantly higher in the large breakfast group. Glucose, insulin (daily, fasting, and oral glucose tolerance test), and HOMA-IR were significantly improved in the large breakfast group. Mean TG concentrations decreased in the large breakfast group, but increased in the large dinner group. The authors concluded that high-calorie breakfasts with reduced intake at dinner might be a useful alternative for management of obese subjects with metabolic disease.

In 2014, Rabinovitz et al. (44) conducted a randomized, treatment-controlled, open clinical trial that evaluated the effect of breakfast size and composition on body weight, glycemic control, and metabolic markers in adults with type 2 diabetes. Fifty-nine overweight or obese adults with type 2 diabetes were randomly assigned to 1 of the following 2 isocaloric diets for 3 mo: a large breakfast rich in fat and protein providing 33% of total daily energy or a small breakfast rich in carbohydrates providing 12.5% of total daily energy. Total daily energy requirements for each subject were calculated and reduced by 500 kcal in order to achieve modest weight loss. Although body weight, BMI, waist circumference, hip circumference, body fat percentage, C-peptide, lipid profile, inflammatory markers (C-reactive protein, IL-6, or TNF-α), and hormonal values (insulin, adiponectin, and cortisol) were reduced similarly in both groups, the large-breakfast group showed greater reductions in fasting and bedtime glucose, glycosylated hemoglobin A1c, systolic blood pressure, and hunger scores. Doses of diabetic medications were also reduced, whereas in the small breakfast group medications were increased. The writers concluded that enriching breakfast with energy as protein and fat appears to have metabolic benefits for type 2 diabetic patients.

Timing of macronutrients. Dietary protein is considered to be a highly satiating macronutrient with the ability to reduce hunger and desire to eat and increase feelings of fullness (45). In a randomized crossover study conducted in 2010 by Leidy and Racki (46), the impact of a protein-rich breakfast on appetite and food intake was evaluated in adolescents who skip breakfast. Adolescents with no known metabolic diseases randomly completed 3 separate testing days that included no breakfast, a normal-protein breakfast, or a protein-rich breakfast. Five hours after breakfast, subjects were provided an ad libitum lunch buffet and completed a food record documenting all food and beverages consumed over the remaining 24 h. The protein-rich breakfast led to a reduction in appetite at lunch vs. no breakfast and the normal-protein breakfast. Fullness was greater after the 2 breakfast meals than after no breakfast, but was not different between meals. Ghrelin concentrations did not differ among treatments. The protein-rich breakfast led to fewer calories being consumed at lunch. Overall, daily food intake was not different among treatments. These findings suggest that the addition of a protein-rich breakfast might be an effective strategy to reduce midday appetite.

An ancient time-related dietary regimen: the religious fast of Ramadan. Fasting during the month of Ramadan is a religious obligation that is practiced by millions of Muslims around the world. It is probably the most ancient recognized food-timing dietary regimen. During Ramadan, all healthy Muslims with the exception of pregnant, lactating, or menstruating women fast during the day and are only allowed to eat and drink from sunset to sunrise. Muslims enjoy a festive atmosphere at sunset and consume large amounts of food and drinks in a high-calorie, carbohydrate-rich meal. Because the Ramadan fast affects a large population, numerous studies have been performed in the last 2 decades evaluating its health impact. It was found that Ramadan fasting leads to changes in metabolic status including blood glucose concentrations, lipid profiles, and body weight. However, results of these studies have been variable, largely because of differences in dietary habits, gender, age, and ethnicity.

A recent systematic meta-analysis conducted by Kul et al. (18) in 2014 used 30 self-controlled cohort studies to answer the question that interests millions of Muslims: "Does Ramadan fasting alter body weight, lipid profiles, and fasting glucose in healthy populations?" The main findings were that

after Ramadan fasting, LDL cholesterol and fasting blood glucose concentrations were decreased compared with concentrations before Ramadan. In the subgroup of women, body weight, total cholesterol, and TG concentrations remained unchanged, whereas HDL cholesterol concentrations were increased. In men, Ramadan fasting resulted in weight loss and a substantial reduction in total cholesterol and LDL cholesterol concentrations and a small decrease in TG concentrations.

Concentrating carbohydrate consumption at dinner: a time-related dietary solution for obesity and metabolic syndrome

Evaluating studies carried out during Ramadan led us to understand that Ramadan is a unique nutritional model. In one study conducted in 46 healthy women who had fasted throughout the month, concentrations of the satiety hormone leptin at midday (normally the lowest point for leptin) were elevated by ~40% (47). In a second study in 10 healthy men, leptin concentrations were measured every 4 h throughout the day. By the end of Ramadan, a marked shift in the daily secretory pattern of leptin was observed (48). Therefore, we speculated that concentrating carbohydrate consumption in the later hours of the day possibly could modify the typical diurnal pattern of leptin secretion as well, leading to higher concentrations of leptin during the early to middle hours of the day, thus enhancing satiety during waking hours rather than at night. Because the secretion of the hunger hormone ghrelin is reciprocally regulated by leptin (49), we also hypothesized that ghrelin's diurnal pattern might be changed after this diet as well. Because ghrelin is involved in inducing hunger, lower concentrations during waking hours could potentially reduce food intake. We believe that, overall, these hormonal changes would lead to improved satiety during waking hours and enhance adherence to the weight-loss diet, resulting in improved anthropometric outcomes. In addition, we anticipated elevated concentrations of adiponectin, a hormone that reduces risk factors for metabolic syndrome that is usually found in low concentrations in obese individuals. This assumption was based on the known negative correlation between insulin and adiponectin (50) and on the fact that our experimental diet allowed no carbohydrate consumption before dinner, thus lowering insulin secretion during the day.

Over the past few years our research group has investigated the effects of a low-calorie diet with carbohydrates eaten only at dinner as a possible time-related dietary approach for severe abdominal obesity and metabolic syndrome (19, 20).

Our study subjects were 78 police officers who were randomly assigned to either a balanced low-calorie diet providing carbohydrates only at dinner (experimental diet) (**Table 1**) or a balanced low-calorie diet with carbohydrates provided at all meals (control diet). Throughout the 6-mo dietary intervention, all study participants met with a dietitian on a regular basis for follow-up. Anthropometric measurements were taken and participants were encouraged to adhere to the dietary regimen. On the first day of the study after an overnight fast, blood samples were taken and questionnaires that rated the hunger and satiety level of the participant were administered. This was repeated every 4 h throughout the day. The same protocol was conducted again after 1 wk, 3 mo, and 6 mo.

TABLE 1 Menu for diet with carbohydrates concentrated at dinner[1]

Breakfast
Coffee or tea with artificial sweetener
Low-fat milk, 1/5 cup (50 mL)
Walnuts, 7 halves or almonds, 7 pieces
Morning snack
Plain low fat yogurt, 1 cup or white cheese, 1/2 cup (125 g)
Vegetables
Lunch
Meat or fish dish (without breading, excluding ground meat)
Boiled vegetables or vegetable soup
Vegetable salad
Oil, 1 tsp (5 mL) or dressing, 1 tbsp (15 mL) (from the permitted list)
Afternoon snack
Coffee or tea with artificial sweetener
Low-fat milk, 1/5 cup (50 mL)
Walnuts, 7 halves or almonds, 7 pieces
Dinner
Coffee or tea with artificial sweetener
Low-fat milk, 1/5 cup (50 mL)
Alternative A or B
Alternative A:
Bread, 2–4 pieces or reduced-calorie bread, 4–8 pieces
White cheese, 1/2 cup (125 g); yellow cheese, 1 slice; hummus, 2 tbsp (30 g); 1 egg; tuna fish, 1/2 can (80 g) or pastrami, 4 slices
Vegetable salad
Oil, 1 tsp (5 mL); tahini, 1 tbsp (15 mL); avocado, 1/4 or dressing, 1 tbsp (15 mL)
Fruit, 1 serving; fruit yogurt, 1 cup; low-calorie ice cream, 1 serving biscuit cookie, 2 or cookie, 1
Alternative B:
Cooked rice, 1–2 cups (150–300 g); pasta, 1–2 cups (100–200 g); mashed potato, 1–2 cups (180–360 g); corn, 1–2 cups (150–300 g); legumes, 1–2 cups (150–300 g); potato, 1 or sweet potato,1
Gravy, 1 tbsp (15 g)
Boiled vegetables or vegetable salad
Oil, 1 tsp (5 g); tahini, 1 tbsp (15 g); avocado, 1/4 or dressing, 1 tbsp (15 g)
Fruit yogurt, 1 cup; low-calorie ice cream, 1 serving; biscuit cookie, 2 or cookie, 1
Night snack
Coffee or tea with artificial sweetener
Low-fat milk, 1/5 cup (50 mL)
Walnuts, 7 halves or almonds, 7 pieces
Plain yogurt, 1 cup or white cheese, 1/2 cup (125 g)

[1] Adapted with permission from (19, 20).

Changes in leptin and ghrelin secretion patterns, hunger and satiety, and anthropometric outcomes. Changes in the diurnal secretion pattern of leptin were observed after the experimental diet. The typical concave diurnal leptin curve, which falls throughout the day with lowest concentrations measured in the afternoon, was replaced on day 180 in the experimental group by a more convex curve with lowest concentrations in the evening. Data for ghrelin were available only for days 7 and 90. Ghrelin's typical diurnal

pattern on day 7 (used as baseline) was convex and included high values at daytime with a peak in the afternoon. This was replaced on day 90 with a concave curve peaking in the evening. It is known that leptin crosses the blood–brain barrier, leading to secretion of anorexigenic pro-opiomelanocortin, which reduces melanin-concentrating hormone and orexin secretion in the lateral hypothalamus, leading to lower wakefulness and food-seeking behavior and reduced food consumption. Simultaneously, leptin inhibits release of the orexigenic neuropeptide Y and agouti-related peptide. Ghrelin also crosses the blood–brain barrier and induces secretion of agouti-related peptide and neuropeptide Y, which promote melanin-concentrating hormone and orexin secretion from the lateral hypothalamus, leading to food consumption (51). Thus, we hypothesized that the hormonal changes observed would improve satiety during the daytime and have a greater impact on anthropometric outcomes in the experimental group. Indeed, it was observed that in individuals consuming carbohydrates only at dinner, after 180 d, hunger and satiety scores were 13.7% higher, indicating that subjects were more satiated than in week 1 of the diet. In contrast, the control group reported a 5.9% lower hunger and satiety score compared with baseline. It was also found that the experimental group felt less hungry in the afternoon on days 90 and 180 and in the evening of day 180 than in week 1 of the study. Anthropometric findings (**Table 2**) showed significantly greater weight loss in the experimental group than in controls. A trend toward greater reduction of BMI was also observed ($P = 0.053$). At the end of the study, the experimental group had improved mean abdominal circumference and mean body fat percentage reductions compared with controls but the differences were not found to be significant.

Changes in adiponectin secretion pattern and metabolic and inflammatory outcomes. At baseline, both diet groups demonstrated low and flat adiponectin curves typical of obese individuals. On day 180, the experimental group curve showed a rise whereas the control group curve was not changed. It is known that adiponectin activates AMP-activated protein kinase (AMPK) in peripheral tissues. As an energy regulator, AMPK reduces energy-consuming anabolic pathways and induces energy-generating catabolic processes.

For example, activation of AMPK reduces gluconeogenetic enzymes in the liver, leading to lower glucose production and lower insulin release. In addition, AMPK deactivates acetyl-CoA carboxylase, promoting FA oxidation in the liver, muscle, and adipose tissues, which in turn decreases serum TGs and enhances insulin sensitivity (52). Adiponectin also activates PPARs, which are nuclear receptors that elevate macronutrient oxidation, improve lipid profile, and regulate inflammation (52–54). Biochemical variables were also markedly improved on day 180 of the intervention (**Table 3**). In experimental subjects, insulin concentrations were significantly reduced compared with controls, and there was a significant decrease in fasting glucose and HOMA-IR. The experimental diet also led to a significant decrease in total cholesterol on day 90; however, the effect was not preserved on day 180. A significant decrease in LDL cholesterol concentrations was found in the experimental group on day 90, whereas on day 180, a significant decrease was measured for each diet. Significant increases in HDL cholesterol were also observed for each diet on days 90 and 180. The experimental HDL cholesterol was significantly greater increased after 180 d compared to control. Furthermore, reductions in inflammatory markers (C-reactive protein, TNF-α, and IL-6) were greater in individuals consuming the experimental diet (Table 3).

Present implications and future directions. Overall, we found that a simple, time-related dietary manipulation led to changes in hormone profiles, improved satiety, greater diligence in the weight loss process, better anthropometric outcomes, increased insulin sensitivity, and improved metabolic and inflammatory status. These results

TABLE 2 Changes in anthropometric variables after experimental and control diets[1]

	Experimental group[2] ($n = 30$)	Control group[3] ($n = 33$)	Comparison between groups
Weight loss			
Kilograms	11.6 ± 0.84*	9.06 ± 0.84*	$P = 0.024$
Percentage	11.7 ± 0.66*	9.96 ± 0.79*	$P = 0.053$
BMI reduction[4]			
Grams per meter squared	3.85 ± 0.25*	3.28+0.24*	$P = 0.115$
Percentage	11.7 ± 0.66*	9.68 ± 0.79*	$P = 0.053$
Abdominal circumference decrease[4]			
Centimeters	11.1 ± 0.92*	10.0 ± 0.88*	$P = 0.408$
Percentage	10.5 ± 0.70*	8.80 ± 0.90*	$P = 0.159$
Body fat percent reduction			
Absolute, %	6.98 ± 0.95*	5.13 ± 0.59*	$P = 0.710$
Relative, %	18.1 ± 2.45*	14.1 ± 1.71*	$P = 0.122$

[1] Values are means ± SEMs, 2-factor ANOVA. *Significant difference from day 0 ($P < 0.0001$). Reproduced with permission from (19).
[2] Received a balanced low-calorie diet providing carbohydrates only at dinner.
[3] Received a balanced low-calorie diet providing carbohydrates throughout the day.
[4] Adjusted for baseline differences.

TABLE 3 Biochemical and inflammatory values and percentage of baseline[1]

Variables	Experimental group[2] (n = 18)		Control group[3] (n = 21)		Comparison of groups
	Absolute mean	% of baseline[4]	Absolute mean	% of baseline[4]	
Insulin, μU/mL					
Day 0	29.8 ± 5.52		23.2 ± 4.48		
Day 90	16.1 ± 1.93	84.4 ± 13.7	20.0 ± 3.61	102.9 ± 13.1	P = 0.332
Day 180	14.9 ± 2.79	68.0 ± 14.3*	16.6 ± 1.63	122.6 ± 12.8	P = 0.006
Glucose, mmol/L					
Day 0	5.10 ± 0.26		4.85 ± 0.25		
Day 90	4.81 ± 0.15	88.6 ± 8.35	4.77 ± 0.08	96.7 ± 6.84	P = 0.454
Day 180	4.71 ± 0.18	80.0 ± 7.53**	4.71 ± 0.16	93.7 ± 6.84	P = 0.184
HOMA-IR					
Day 0	1.68 ± 0.24		1.33 ± 0.20		
Day 90	1.14 ± 0.15	69.1 ± 15.8	1.33 ± 0.16	119.7 ± 12.8	P = 0.015
Day 180	1.09 ± 0.12	89.0 ± 15.2	1.20 ± 0.15	121.3 ± 13.2	P = 0.114
TGs, mmol/L					
Day 0	1.88 ± 0.17		2.00 ± 0.17		
Day 90	1.22 ± 0.09	69.2 ± 7.20***	1.22 ± 0.14	65.8 ± 5.92***	P = 0.717
Day 180	1.20 ± 0.13	70.6 ± 6.95***	1.33 ± 0.17	68.7 ± 6.00***	P = 0.834
Total cholesterol, mmol/L					
Day 0	5.46 ± 0.18		5.02 ± 0.15		
Day 90	4.94 ± 0.17	91.9 ± 2.63**	4.76 ± 0.18	95.7 ± 2.45	P = 0.290
Day 180	5.32 ± 0.23	97.6 ± 2.75	4.87 ± 0.18	96.3 ± 2.48	P = 0.733
LDL cholesterol, mmol/L					
Day 0	3.66 ± 0.18		3.14 ± 0.15		
Day 90	3.29 ± 0.18	89.0 ± 3.52**	3.18 ± 0.15	97.8 ± 3.28	P = 0.073
Day 180	3.43 ± 0.22	90.3 ± 3.70*	3.00 ± 0.13	92.43.26*	P = 0.670
HDL cholesterol, mmol/L					
Day 0	0.78 ± 0.06		0.83 ± 0.05		
Day 90	0.88 ± 0.04	114.3 ± 4.48**	0.91 ± 0.04	110.4 ± 4.18*	P = 0.525
Day 180	1.07 ± 0.09	140.8 ± 4.65***	1.05 ± 0.05	126.0 ± 4.16***	P = 0.022
CRP, mg/L					
Day 0	8.2 ± 2.0		3.4 ± 0.6		
Day 90	5.6 ± 1.6	99.0 ± 19.8[5]	2.5 ± 0.4	98.3 ± 19.1[5]	P = 0.979
Day 180	3.9 ± 1.1	72.2 ± 20.8[5]	2.2 ± 0.4	94.2 ± 19.5[5]	P = 0.456
TNF-α, pg/mL					
Day 0	1.89 ± 0.15		1.93 ± 0.24		
Day 90	1.85 ± 0.18	101.4 ± 8.39	2.14 ± 0.29	117.3 ± 7.80*	P = 0.169
Day 180	1.65 ± 0.16	90. 8 ± 8.82	2.12 ± 0.33	116.2 ± 7.78*	P = 0.034
IL-6, pg/mL					
Day 0	2.71 ± 0.33		2.52 ± 0.26		
Day 90	2.22 ± 0.33	84.8 ± 13.4	2.06 ± 0.27	91.5 ± 11.9	P = 0.710
Day 180	1.61 ± 0.21	63.0 ± 13.4**	1.84 ± 0.20	76.3 ± 12.2	P = 0.465

[1] Values are least squares means ± SEs. Insulin, glucose, HOMA-IR, TGs, CRP, TNF-α, and IL-6 are percentages from day 0. Total cholesterol, LDL cholesterol, and HDL cholesterol are percentages from days 0 and 7. Asterisks indicate significantly different from baseline as follows: *$P < 0.05$, **$P < 0.01$, ***$P < 0.0001$. Reproduced with permission from (19). CRP, C-reactive protein.

[2] Received a balanced low-calorie diet providing carbohydrates only at dinner.

[3] Received a balanced low-calorie diet providing carbohydrates throughout the day.

[4] Calculated for each subject and averaged.

[5] Adjusted for baseline differences.

support a simple dietary alternative that may provide long-term benefits for people with abdominal obesity and metabolic syndrome.

In order to further understand and characterize the pathways and metabolites responsible for the positive findings of our clinical studies, experiments are underway in our laboratory with the use of animal models. We are examining changes in neural hypothalamic pathways that control body weight and food intake after consumption of our experimental diet and studying the mechanisms that allow this nutritional approach to facilitate maintenance of long-term weight loss. Investigation of changes in key metabolic variables in the peripheral tissues are also being performed in order to elucidate the mechanisms that beneficially affect metabolic syndrome.

Conclusions

Fighting the vicious cycle of abdominal obesity and metabolic syndrome by nutrition targeting is an important undertaking of scientists and dietitians. Based on the data discussed, it is clear that restricted-calorie diets can reduce weight and improve metabolic markers but, for the most part, are difficult to maintain over the long term with positive health outcomes not usually preserved. Diets that focus on specific macronutrients do not appear to have any particular advantage with respect to anthropometric or biochemical outcomes and

long-term maintenance. It is well established that the traditional Mediterranean diet can ameliorate metabolic syndrome and the risk of developing type 2 diabetes and cardiovascular disease. However, this diet has not been proven effective against the vicious cycle of abdominal obesity without calorie restriction and increased physical activity. The evidenced-based DASH demonstrated a primary effect on blood pressure and cardiovascular disease but does not fully address abdominal obesity and other risk factors for metabolic syndrome.

Timing of food consumption, meals, and macronutrients is a new tactic to address the problem of obesity and metabolic syndrome. It appears that eating with the correct restricted meal timing and macronutrient distribution might be part of the solution. In our studies with carbohydrates concentrated at dinner, we demonstrated improved satiety along with better anthropometric, metabolic, and inflammatory status. We conclude that this dietary regimen might offer an innovative, time-related method of nutrition targeting for abdominal obesity and metabolic syndrome. Further research is needed in order to confirm our results and better understand the underlying mechanisms of action.

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