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CLINICAL TRIALS: BEHAVIOR, PHARMACOTHERAPY, DEVICES, SURGERY

Obesity

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High Caloric Intake at Breakfast vs. Dinner Differentially Influences Weight Loss of Overweight and Obese Women

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Objective: Few studies examined the association between time-of-day of nutrient intake and the metabolic syndrome. Our goal was to compare a weight loss diet with high caloric intake during breakfast to an isocaloric diet with high caloric intake at dinner.

Design and Methods: Overweight and obese women (BMI 32.4 ± 1.8 kg/m^2) with metabolic syndrome were randomized into two isocaloric (~1400 kcal) weight loss groups, a breakfast (BF) (700 kcal breakfast, 500 kcal lunch, 200 kcal dinner) or a dinner (D) group (200 kcal breakfast, 500 kcal lunch, 700 kcal dinner) for 12 weeks.

Results: The BF group showed greater weight loss and waist circumference reduction. Although fasting glucose, insulin, and ghrelin were reduced in both groups, fasting glucose, insulin, and HOMA-IR decreased significantly to a greater extent in the BF group. Mean triglyceride levels decreased by 33.6% in the BF group, but increased by 14.6% in the D group. Oral glucose tolerance test led to a greater decrease of glucose and insulin in the BF group. In response to meal challenges, the overall daily glucose, insulin, ghrelin, and mean hunger scores were significantly lower, whereas mean satiety scores were significantly higher in the BF group.

Conclusions: High-calorie breakfast with reduced intake at dinner is beneficial and might be a useful alternative for the management of obesity and metabolic syndrome.

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Introduction

The metabolic syndrome is a combination of several abnormalities, including abdominal obesity, glucose intolerance, hypertension, and dyslipidemia that share insulin resistance as a common underlying pathophysiological disturbance (1). The metabolic syndrome is associated with the risk of type 2 diabetes, cardiovascular disease, and all-cause mortality (2). The key therapeutic approach is a weight loss diet focused on the daily caloric intake and nutrient composition. However, current evidence suggests that the time-of-day of nutrient intake can also influence the metabolic syndrome by affecting circadian rhythms (3-6).

Circadian rhythms are driven by the master clock localized in the suprachiasmatic nuclei (SCN), which is synchronized by the everyday light–dark cycle (7). Similar clocks are found in peripheral tissues, such as adipose tissue, liver, and gut (8-10). The clock mechanism in the brain and peripheral tissues regulates the circadian expression and activity of enzymes and hormones involved in metabolism (6,11,12). As a result, disruption of circadian rhythms leads to hyperphagia, obesity, and insulin resistance (13-15).

Meal timing and feeding schedule exert strong entraining effects on peripheral oscillators over-riding rhythmic signals transmitted by the SCN (16,17). Meal timing has crucial implications on weight gain, appetite, and glucose and lipid metabolism (3-6,18). Indeed, skipping breakfast and/or overeating in the evening, play a significant role in weight gain and obesity (19-21). It was shown in animals that the daily first meal (equivalent to breakfast) determines the circadian phase of peripheral clocks, whereas the last meal (equivalent to dinner) leads to lipogenesis and adipose tissue accumulation (5). Moreover, it was shown in breakfast skippers that the activation of lipolysis was delayed, whereas lipogenesis increased (22,23). These data are congruent with previous studies reporting that patients with night-eating habits are inclined to being obese (24). We recently showed that the same caloric intake in a different time window during the day led to a different body weight, emphasizing the role of clock resetting in energy homeostasis (25).

Meal composition, in addition to timing, also appears to influence satiety. Specifically, protein consumed at breakfast (compared to

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TABLE 1 Meal breakdown and nutritional values

	Qty	Energy (kcal)	Proteins (g)	Fat (g)		Carbohydrates (g)			Sodium (mg)	Cholesterol (mg)
				Total	Saturated	Total	Fiber	Sugars		
Large										
Whole-wheat bread	2 slices	136	5.4	2.4	0.5	25.8	3.9	11.1	295	
Light Tuna in water	4 oz	120	26	1		1	0.4		460	50
Skim milk	16 fl oz	160	16.4	0.4	0.6	24.4		24	216	10
Milk chocolate	1 bar	210	3	13	8	26	1	24	35	10
Sweet tomato, basil and mozzarella salad	1/2 cup	60	2	4.5	1	3.5	0.5	1	90	5
Americano	1 grande	15	1			3			10	
Total		**701**	**53.8**	**21.3**	**10.1**	**83.7**	**5.8**	**60.1**	**1106**	**75**
Percentage of calories			**29%**	**26%**	**12%**	**45%**		**32%**		
Medium										
Grilled Chicken breast	5 oz	236	44.3	5.1	1.4				106	121
Melons	1 cup	54	1.3	0.3	0.1	13.1	1.4	12.6	26	
Diet coca-cola	12 fl oz								40	
Light mayonnaise	1 tbsp	50	0.1	4.9	0.8	1.3		0.6	120	5
Beef broth soup	1 can	71	13			4.3			1550	
Green salad w/ balsamic vinaigrette	1 cup	91	2	7	1	7	1	5	59	3
Total		**502**	**60.7**	**17.3**	**3.3**	**25.7**	**2.4**	**18.2**	**1901**	**129**
Percentage of calories			**48%**	**31%**	**6%**	**21%**		**15%**		
Small										
Scrambled egg whites	2 eggs	100	12	6		2			180	
Americano	1 large	15				2		2	30	
Turkey breast	5 slices	100	23.3			1.7			92	40
Total		**215**	**35.3**	**6**		**5.7**		**2**	**302**	**40**
Percentage of calories			**65%**	**25%**		**10%**				
Total		**1418**	**149.8**	**44.6**	**13.4**	**115.1**	**8.2**	**80.3**	**3309**	**244**
Percentage of Calories†			**41%**	**27%**	**8%**	**32%**		**22%**		

lunch or dinner) leads to greater initial and sustained feeling of fullness, increased satiety and reduced concentrations of the appetite-regulating hormone ghrelin (20,21,26,27). Recently, we have shown that compared to a low-carbohydrate diet, an isocaloric diet with high-calorie breakfast promoted sustained weight loss with ghrelin suppression and reduced diet-induced compensatory changes in food cravings (26). Also, increasing carbohydrate intake in the morning has been suggested to have a long-term protective effect against the development of metabolic syndrome (28). However, few studies examined the association between time-of-day of nutrient intake and the metabolic syndrome. This study was conducted to test whether a change in meal timing, switching between a high-calorie breakfast and a high-calorie dinner, with an overall similar daily caloric intake has a different impact on weight loss, appetite scores, and other characteristics of the metabolic syndrome.

Methods

Study design

We used a randomized, open-label, parallel-arm study design in which patients received dietary advice to one of the two isocaloric weight loss diets for 12 weeks. Nurses at the clinical unit were assigned to randomly enroll participants to interventions using a single allocation ratio. The protocol and potential risks and benefits of the study were fully explained to each subject. The study was approved by the Institutional Helsinki Ethics Committee and written informed consent was obtained from each subject before entry into the study. The study start date for recruiting participants was June 2012 and continued until October 2012. The study was completed in January 2013. The two meal plans were either high-calorie breakfast (BF) or high-calorie dinner (D) with a total daily energy of 1400 ± 25 kcal with identical macronutrient content and composition. The energy of the BF meal plan was: a large breakfast (~700 kcal, 50%), medium-sized lunch (~500 kcal, 36%), and a small dinner (~200 kcal, 14%) (Table 1). This was reversed in the D meal plan; a small breakfast and a large dinner. An example of the content of the different meals is given in Table 1. Subjects were provided with proper food replacement choices for each food item to allow variation. Subjects were asked to eat breakfast at 6:00-9:00, lunch at 12:00-15:00, and dinner at 18:00-21:00. Additionally, by the end of the second week, the assigned breakfast, lunch, and dinner meal-tolerance tests were performed.

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Subjects

The study protocol initially included a total of 93 obese/overweight women (age range: 30-57, 45.8 ± 7.1 years), with the metabolic syndrome recruited from outpatient clinics by means of personal interview or advertising. The women were eligible if they were adults (age 20-65 years), overweight or obese (BMI 25-37 kg/m^2), nondiabetic [glucose < 200 mg/dl 2 h after oral glucose tolerance test (OGTT)] and met ≥ 3 of 5 National Cholesterol Education Program Adult Treatment Panel III criteria for metabolic syndrome (1). Those with abnormal thyroid, liver or kidney function, cardiovascular disease, cancer, or any other serious medical condition, those using any medications known to affect glucose, insulin, or reproductive hormones, or those who were pregnant or lactating were excluded. Individuals who were presently dieting, using medications affecting body weight or who had experienced a change in weight >4.5 kg or a change in physical activity within the six months preceding the study onset were excluded. Subjects with gastrointestinal problems deemed likely to interfere with participation in or compliance with the study were also excluded. Subjects taking antihypertensive or lipid-lowering medication were asked to maintain all medications and supplements at pre-study doses. Subjects were sedentary at baseline and were asked to maintain their usual physical activity levels and document and report a change in their activity level every 2 weeks.

Dietary assessment and compliance

The participants provided a weekly 3-day record but were instructed to make additional notes if they deviated from the assigned diet on the nonrecorded days. The dietitian, during her biweekly consult, with the aid of the records and interview, had an idea about their adherence to the diet. The dietitian reviewed the diet records with each participant and shared the diet analysis with him or her at the next biweekly visit. Diet records were analyzed with USDA National Nutrient Database for standard reference. Compliance assessment was based on subject adherence to dietary instruction as indicated by the assigned meal plan. Noncompliance was defined as a deviation of 10% or more from the recommended energy intake. Thus, for a diet of ∼1400 cal/day, when energy intake on a given day exceeded 1540 kcal, a noncompliance event was recorded. During a 12-week intervention, a given individual could conceivably contribute approximately 84 noncompliance events. In each of the diets, the number of days for which participants were noncompliant, were divided by seven during which participants were in the program, yielding a weekly percentage of noncompliance. Those participants with weekly noncompliance equal or above 42.9% (noncompliance of >3 days per week) were withdrawn from the study.

Clinical and anthropometric measurements

Body weight, blood pressure, and waist circumference were recorded every 2 weeks. Body weight was measured by using a scale model Detecto Physician Beam Scale (HOSPEQ, Inc., Miami, FL). Waist circumference was measured by the same person according to the guidelines of the National Heart, Lung, and Blood Institute (NIH publication no. 00-4084). Blood pressure was measured with the use of an automatic blood pressure monitor (Omron Healthcare, Milton Keynes, UK).

Blood samples

OGTT was performed for both BF and D groups at baseline and at the end of the study (week 12) with a 75-g oral glucose challenge. Fasting blood samples were collected in the morning after a 12-h fast. Two-hour blood samples were taken at 30, 60, 90, and 120 min for the measurement of serum glucose and insulin. Serum was separated by centrifugation for 15 min at 1465 × *g* (3200 rpm) at 4°C and stored at −80°C until further analysis.

Breakfast, lunch, and dinner meal challenge

On the day of meal challenge, each subject is reported to the laboratory at 07:00 after an overnight fast. At 07:30, a catheter was placed in the antecubital vein of the nondominant arm and remained in the patient until 20:00. Fasting baseline blood sample was taken for measurement of glucose, insulin, and ghrelin. Each group consumed their assigned meal plan (Table 1), breakfast at 8:00, lunch at 13:00, and dinner at 19:00. The test meals were consumed in their entirety within 15 min. Venous blood samples were collected 30, 60, 120, and 180 min after breakfast, lunch, and dinner for glucose, insulin, and ghrelin. The appetite visual analogue scale scores (hunger and satiety) were concomitantly completed.

Appetite questionnaires

Appetite scores for hunger and satiety were assessed using 100-mm visual analogue scales (29) before and 30, 60, 120, and 180 min after breakfast, lunch, and dinner. Subjects were asked to make a single vertical mark on each scale somewhere between the 0 and 100 mm extremes (i.e., not at all hungry to very hungry) to indicate their feelings at that time-point.

Biochemical blood analyses

Serum glucose was determined by the glucose oxidase method (Beckman Glucose Analyzer, Fullerton, CA). Total and HDL cholesterol and triacylglycerols were measured enzymatically using a Hitachi-Cobas Bio centrifugal analyzer (Roche Diagnostics, Indianapolis, IN) using standard enzymatic kits (Roche Diagnostics). Low-density lipoprotein cholesterol (LDL-C) concentrations were calculated using the Friedewald equation as was described earlier (30). Serum insulin was determined by a double antibody radioimmunoassay (CIS Bio International, Gif-Sur Yvette-Cedex, France). Plasma ghrelin was measured with an enzyme immunoassay kit (Phoenix Pharmaceuticals, Belmont, CA). Homeostasis model assessment indices of insulin resistance (HOMA-IR) and beta-cell (HOMA-B) function were calculated using the following formulas: HOMA-IR = fasting serum insulin (μIU/ml) × fasting serum glucose (mmol/l)/22.5; HOMA-B = 20 × fasting serum insulin (μIU/ml) / fasting glucose (mmol/l)-3.5 (31). Insulin sensitivity index (ISI) was calculated using the following formula: ISI = 10,000/$\sqrt{}$((fasting glucose (mg/dl) × fasting insulin (μIU/ml)) × (mean glucose (mg/dl) × mean insulin (μIU/ml))) (32).

Sample size and power analysis

A sample size of 50 participants was planned (25 in each treatment group) provided 90% power to detect a true ($P < 0.05$) between-group difference of 5 ± 10 kg at the end of the follow-up. Additional 43 subjects were recruited to cover drop outs, which were predicted to reach approximately 50% based on diet study drop-out rates in the literature.

Statistical analysis

All results are expressed as mean ± SE. For time series, ANOVA (time × treatment) was performed and a least-significant difference

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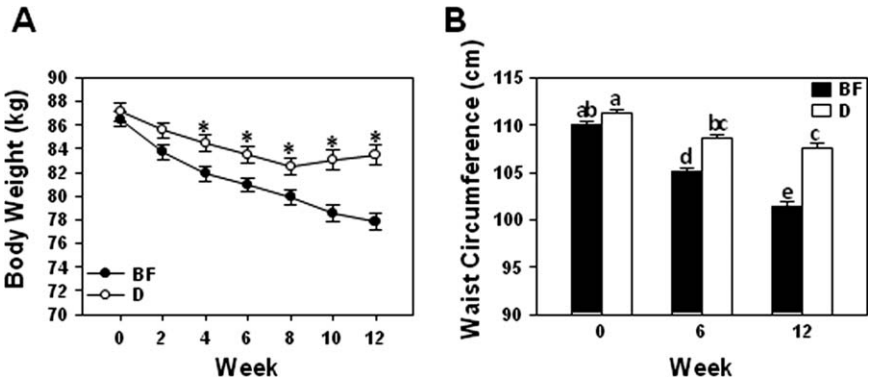

FIGURE 1 Body weight and waist circumference in the BF and D groups. (**A**) Body weight was recorded every 2 weeks for 12 weeks and (**B**) waist circumference was measured at the beginning, after 6 weeks and at the end of the experiment. Values are means ± SE; BF, breakfast group; D, dinner group; *denotes $P < 0.05$; Different letters denote significant difference $P < 0.05$.

t-test post-hoc analysis was used for comparison between the treatments at each time-point. One-way ANOVA followed by Tukey-Kramer post-hoc analysis was performed for multiple comparisons. Statistical analysis was performed with JMP software (version 9, SAS Institute, Cary, NC).

Results

Patient compliance and dispensation

Ninety three overweight and obese women (BMI 32.2 ± 1.2 kg/m^2), aged 45.8 ± 7.1 years, were randomized to two meal plans of a weight loss diet (~1400 kcal) during 12 weeks. Forty six women were assigned to the breakfast (BF) meal plan and 47 women were assigned to the dinner (D) meal plan. Both meal plans had the same composition but differed in energy intake throughout the day. This approach with different meal sizes of the same diet and with identical daily macronutrient composition decreased the variation because of the change in food types. Noncompliance of energy intake, defined as 10% deviation or more from the recommended energy intake, did not differ between the groups and did not correlate with weight and BMI (data not shown). Dropout from the study was mainly because of poor ability to follow dietary instructions. In the BF group eight (17%) dropped out and 38 completed the study, whereas form the D group 11 (23%) dropped out and 36 completed the study. Noncompliance of energy intake in drop-outs was significantly greater only in the D group, whereas weight loss was significantly greater in patients who completed the study in both group (data not shown).

Weight loss, waist circumference, and blood pressure of BF or D meal plan groups

Body weight decreased significantly ($P < 0.0001$) in both the BF and D groups over 12 weeks. However, compared with the D group, the BF group showed a 2.5-fold greater weight loss (−8.7 ± 1.4 vs. −3.6 ± 1.5 kg, respectively) (One-way ANOVA $P < 0.0001$) (Figure 1A, Table 2). As a result, the BMI was significantly different between the groups ($P < 0.0001$, post-hoc Tukey Kramer), with 10% reduction in the BF group and only 5% reduction in the D group (Table 2). Participants assigned to the BF plan also showed a greater reduction in waist circumference than participants assigned to the D plan, both at 6 and 12-week follow-ups (−8.5 ± 1.9 vs. −3.9 ± 1.4 cm, respectively) ($P < 0.0001$, post-hoc Tukey Kramer) (Figure 1B). Systolic and diastolic blood pressures were not significantly different at week 0, but both significantly decreased ($P < 0.0001$, One-way ANOVA) with no significant difference between the BF and the D groups ($P > 0.05$, post-hoc Tukey Kramer) (Table 2). Overall, the BF group showed greater reduction in BMI and waist circumference than the D group.

Fasting serum glucose, insulin, ghrelin, and lipids of BF or D meal plan groups

At baseline, both groups were similar in serum glucose, total cholesterol, HDL, LDL-C, triglycerides, and plasma ghrelin concentrations (Table 2). After 12 weeks, mean serum triglyceride concentrations decreased by 33.6% in the BF group, but increased by 14.6% in the D group ($P < 0.0001$, post-hoc Tukey Kramer). Total cholesterol slightly but significantly decreased and HDL-cholesterol slightly but significantly increased only in the BF group ($P < 0.0001$, post-hoc Tukey Kramer) (Table 2). Serum insulin concentrations and HOMA-IR were lower ($P < 0.0001$, post-hoc Tukey Kramer) at baseline in the D group. However, HOMA-B, a beta-cell function index, did not differ between the groups (Table 2). After 12 weeks, fasting glucose, insulin, ghrelin concentrations as well as HOMA-IR and HOMA-B were reduced in both BF and D groups. However, fasting glucose, insulin, and HOMA-IR decreased to a greater extent in the BF group compared to the D group ($P < 0.0001$, post-hoc Tukey Kramer) (Table 2). It is noteworthy that although insulin and HOMA-IR baseline levels were higher in the BF group, the extent of reduction in this group led to significantly lower levels compared to the D group. In contrast with HOMA indices, the ISI index of insulin sensitivity increased in both BF and D groups, indicating an improvement in insulin sensitivity. However, the BF group showed a greater ISI increase compared with the D group.

OGTT response in BF or D meal plan groups

At baseline, fasting serum glucose and insulin concentrations did not differ between the BF and D groups in response to OGTT

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TABLE 2 Participants anthropometric and blood measurements

	Week 0		Week 12		Change %	
TREATMENT	BF group	D group	BF group	D group	BF group	D group
N	46	47	38	36		
Age (yr)	45.1±1.1	46.5±1	45.6±1.2	46.2±1.2	NS	NS
Anthropometric measurements						
Height (cm)	163.6±0.5	164.5±0.5	163.4±0.6	164.4±0.6	NS	NS
Weight (kg)	86.5±0.7^{ab}	87.1±0.7^{a}	77.8±0.7^{c}	83.5±0.8^{b}	-11%	-4%
BMI (kg/m^2)	32.3±0.2^{a}	32.2±0.2^{a}	29.2±0.2^{c}	30.9±0.2^{b}	-10%	-5%
Waist circumference (cm)	110.1±0.40	111.2±0.41	101.4±0.43	107.6±0.51	-7.9%	-3.2
Blood pressure						
Systolic (mmHg)	133.9±0.6^{a}	132.1±0.7^{a}	125.1±0.7^{b}	127.6±0.7^{b}	-6.5%	-3.4%
Diastolic (mmHg)	88.4±0.5^{a}	87.3±0.4^{a}	82.4±0.5^{b}	84.1±0.4^{b}	-6.7%	-3.6%
Lipids						
Triglycerides (mg/dl)	179.7±2.6^{b}	178.1±3.6^{b}	119.4±2^{c}	204.1±3.7^{a}	-33.6%	+14.6%
Total cholesterol (mg/dl)	215.7±2.4^{a}	220.2±2.5^{a}	203.9±2.5^{b}	217.6±2.1^{a}	-5.40%	NS
LDL (mg/dl)	133.3±2.4	137.0±2.5	130.8±2.4	129.7±2.3	NS	NS
HDL (mg/dl)	46.5±0.6^{b}	47.6±0.7^{ab}	49.2±0.8^{a}	47.1±0.8^{ab}	5.8%	NS
Fasting glucose, insulin and ghrelin						
Glucose (mg/dl)	94.6±0.9^{a}	92.9±0.7^{a}	83.7±0.7^{c}	89±0.9^{b}	-11.5%	-4.2%
Insulin (μIU/ml)	20.2±0.4^{a}	18.6±0.5^{b}	9.9±0.2^{d}	13.2±0.2^{c}	-51%	-29%
Ghrelin (pg/ml)	569±6^{a}	565±6^{a}	518±7^{b}	537±10^{b}	-9%	-4.9%
Insulin sensitivity indices						
HOMA-IR	4.7±0.1^{a}	4.3±0.1^{b}	2.0±0.0^{d}	2.9±0.1^{c}	-57%	-32.5%
HOMA-B	239±8^{a}	229±8^{a}	180±7^{b}	190±7^{b}	-25%	-17%
ISI	2.33±0.03^{c}	2.49±0.04^{c}	6.13±0.09^{a}	3.90±0.06^{b}	+163%	+56%

Different letters denote significant difference; BF, breakfast; D, dinner, NS, nonsignificant

(Figure 2A and B). However, after 12 weeks, both glucose and insulin excursions were significantly lower in the BF group compared with the D group (Figure 2A and B). The changes were reflected in the $AUC_{glucose}$ and $AUC_{insulin}$ after 120 min that were lower at week 12 compared to baseline (Figure 2C and D). The extent of reduction of $AUC_{glucose}$ and $AUC_{insulin}$ was significantly greater in the BF group (−22% and −58%, respectively) compared with the D group (−15% and −30%, respectively) ($P < 0.0001$, post-hoc Tukey Kramer) (Figure 2C and D).

Breakfast, lunch, and dinner meal challenge of BF or D groups

Test meals were selected to be performed on the second week because the subjects were already on the diet and to prevent the effect of weight reduction. At baseline, fasting serum glucose and insulin concentrations did not differ between the groups (Figure 3A). Serum glucose and insulin response to the high-calorie dinner meal test in the D group were significantly higher compared to serum glucose and insulin response to high-calorie breakfast meal of the BF group (Figure 3B). After lunch and dinner meal tests the glucose and insulin concentrations and AUCs of the BF group were lower than those of the D group (Figure 3A and B). Plasma ghrelin concentrations did not differ at baseline; they remained relatively high and constant throughout the day in the D group. In the BF group plasma ghrelin concentrations dropped during breakfast and increased throughout the day, but never reached the concentrations of the D group as reflected in the AUC (Figure 3A and B). The findings with ghrelin are mirrored by the hunger and satiety scores, i.e., decreased hunger and increased satiety in the BF group throughout the day with constant high hunger scores and lower satiety scores in the D group (Figure 3A and B). Interestingly, the lunch challenge, which was similar in both groups, led to a smaller postprandial increase in glucose and insulin, to a greater reduction in ghrelin and hunger scores and increased satiety scores in the BF group compared with the D group. The overall daily response to breakfast, lunch, and dinner challenge meals, expressed as $AUC_{glucose}$ $AUC_{insulin}$, $AUC_{ghrelin}$, and mean daily hunger levels, was significantly lower by 7%, 25%, 24%, and 28%, respectively, in the BF group compared to the D group ($P < 0.0001$, One-way ANOVA). In contrast, mean daily satiety levels were 31% higher in the BF group compared to the D group ($P < 0.0001$, One-way ANOVA) (Figure 3).

Discussion

In this study, the effect of timed caloric intake (high calorie in the morning vs. high calorie in the evening) with an overall similar daily caloric intake was tested. We show that an isocaloric weight loss diet with exchanged caloric intake between breakfast and dinner differentially influences weight loss, waist circumference, serum ghrelin and lipids, appetite scores, and insulin resistance indices in

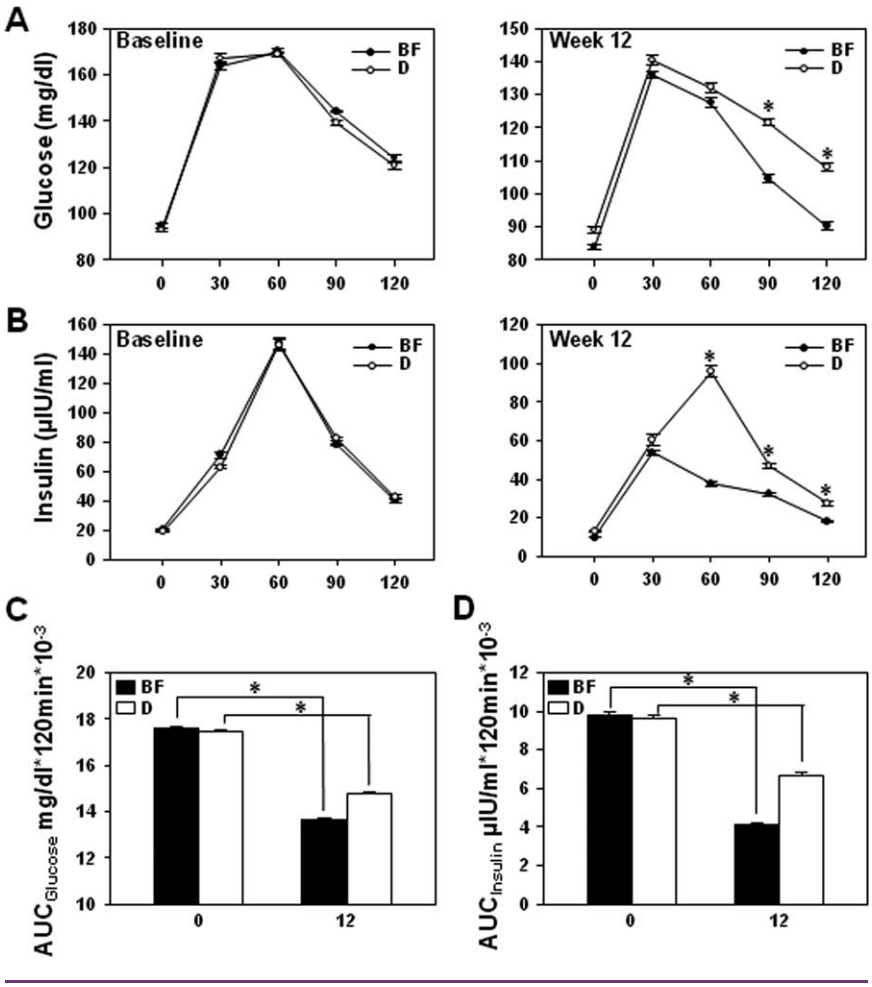

FIGURE 2 The effect of OGTT in the BF and D groups. (**A**) Blood glucose and (**B**) insulin at baseline and at week 12 were measured every 30 min and (**C,D**) AUC was calculated. OGTT (75 g) was performed at baseline and after 12 weeks. Values are means ± SE; BF, breakfast group; D, dinner group; * denotes $P < 0.05$.

overweight and obese women with the metabolic syndrome. We selected 1400 ± 25 kcal intake for the weight loss diet, since our previous study showed that a similar daily caloric intake in women with high-calorie breakfast, resulted in successful weight loss maintenance, ghrelin suppression, and improved appetite scores (26).

The greater weight loss and reduction in waist circumference in the BF group is consistent with previous cross-sectional studies that indicate that regular breakfast consumption leads to reduced BMI and body fat (33,34). The greater reduction in waist circumference in the BF group is particularly important as elevated waist circumference is a determinant of insulin resistance and cardiovascular disease risk (2). Indeed, it was recently shown that among the components of the metabolic syndrome, waist circumference is influenced mostly by the time-of-day of nutrient intake (28). As the breakfast in the BF group was particularly high in carbohydrates, these results are congruent with previous findings that carbohydrate intake at breakfast is protective against abdominal obesity (28).

Although both BF and D meal plans led to reduced fasting glucose and insulin concentrations as well as HOMA-IR and HOMA-B, the BF group showed increased reduction in fasting glucose, insulin, and HOMA-IR compared with the D group. The BF group also showed greater reduction in mean serum triglyceride and total cholesterol concentrations and increase in HDL-cholesterol, whereas in the D meal group, despite the weight loss, an increase in serum triglycerides concentration was observed. Consistent with these results, it was previously shown a relatively impaired postprandial glucose and lipid tolerance following meals consumed at night (35). In contrast, high carbohydrate intake at breakfast was negatively related with triglyceride concentrations (28). It is noteworthy that the effect on insulin resistance is not because of the hypocaloric diet in this study, as lean women with polycystic ovary syndrome (PCOS) who consumed a weight maintenance diet with high caloric intake at breakfast and reduced intake at dinner resulted in improved insulin sensitivity indices compared to a matching dinner group (J.D, O.F, unpublished results).

Importantly, the isocaloric meal plans differentially influenced glucose, insulin, ghrelin, and hunger and satiety responses. Specifically, the highest glucose and insulin values were observed after a high-calorie dinner consumed by the D group compared with an

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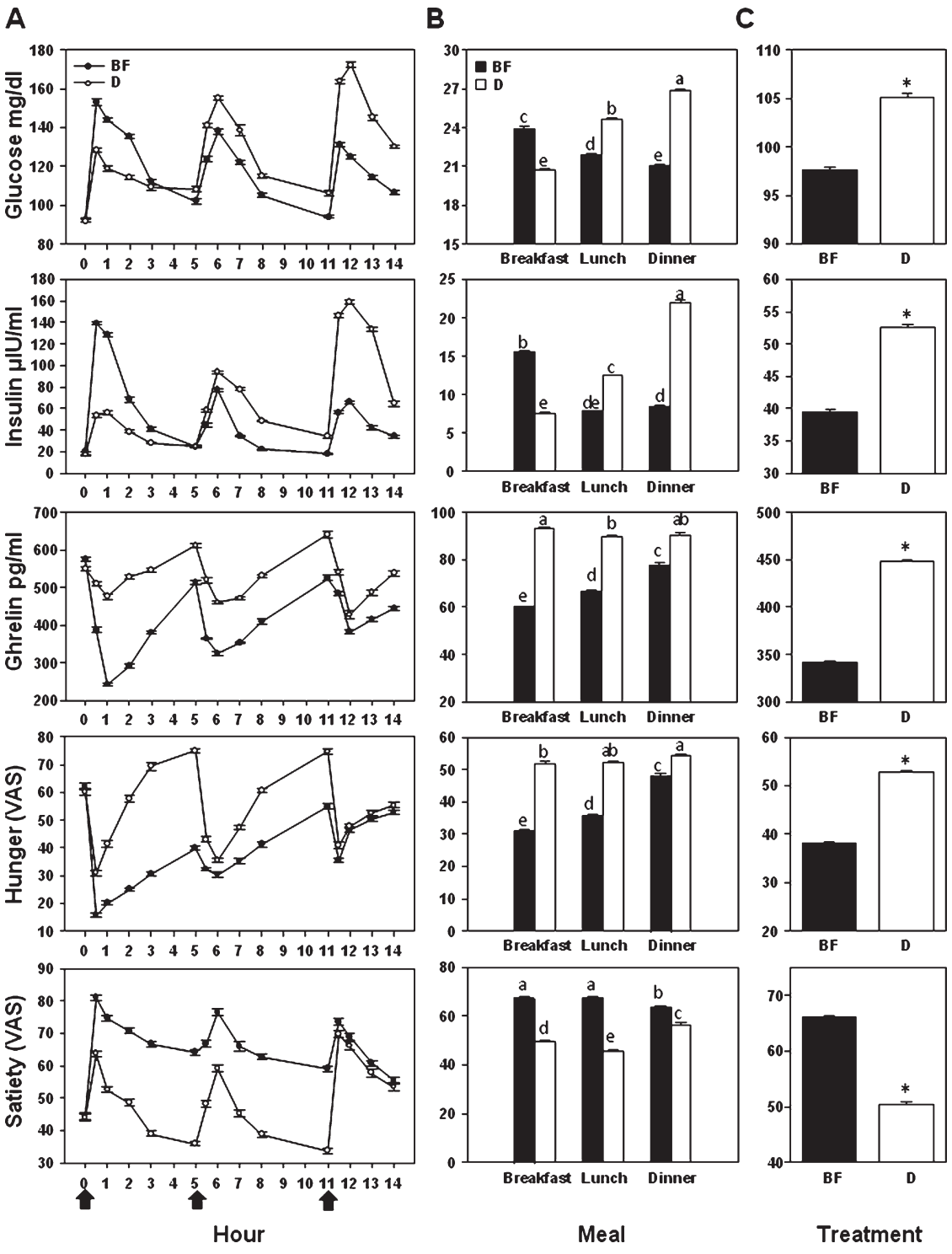

FIGURE 3 The effect of meal challenge on glucose, insulin and ghrelin levels in the BF and D groups. Meal test challenge was performed on a single day during the second week of the study. Each group consumed their assigned diet, blood samples were collected before and 30, 60, 120, and 180 min after each meal and appetite visual analogue scales for hunger and satiety were completed. (**A**) Daily changes of circulating glucose, insulin and ghrelin, and satiety and hunger scores. Meals were served at the times designated by the arrows. (**B**) Meal AUC for circulating glucose, insulin and ghrelin, and mean scores for each meal calculated at 0-180 min following meal consumption. Bars not denoted by the same letter are significantly different. (**C**) Daily AUC for circulating glucose, insulin and ghrelin, and mean daily scores calculated for each group. Values are means ± SE; BF, breakfast group; D, dinner group; * denotes $P < 0.05$; Different letters denote significant difference $P < 0.05$.

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isoenergetic meal consumed at breakfast in the BF group. This is consistent with previous studies that have shown that insulin sensitivity and glucose tolerance decreases progressively throughout the day with insulin sensitivity reaching a nadir in the evening (18,36,37). This may also explain why evening or night eating is often associated with weight gain and obesity (38). We also found that despite the same caloric intake at lunch, serum glucose and insulin responses were significantly lower in the BF group, suggesting a protective effect against postprandial hyperinsulinemic response after the second meal (39). As a consequence, the overall daily AUC of glucose and insulin were significantly lower in the BF group than in the D group. After 12 weeks, OGTT yielded lower glucose and insulin excursions in the BF group compared with the D group. Although these results are congruent with the daily glucose and insulin levels, it is possible that the BF participants were more accustomed to large quantities at the morning meal. Therefore, we can speculate that the decrease in the overall insulin concentrations throughout the day in the BF group may be protective against the development of the metabolic syndrome and its complications. This is also consistent with a previous study that showed that the nutrient composition of different eating occasions predicts metabolic syndrome development (28).

The greater satiety scores paralleled by higher ghrelin suppression after the high-caloric breakfast in the BF group were associated with increased compliance in this group compared with the D group. This reiterates previous studies that correlated breakfast and its content, i.e., protein and carbohydrates, with high satiety scores (20,21,26-28). Our findings also support a strong correlation between the timing of food intake and body weight. The association with feeding time has been shown in various organisms as a strong time giver for the circadian clock (6,16). As the circadian clock and metabolism are tightly linked (12), and disruption of circadian rhythms leads to obesity (13), it is plausible that energy intake and content at different times, i.e., breakfast vs. dinner, may affect the clock differently. Indeed, morning diet-induced thermogenesis (DIT) was significantly higher than afternoon and night DIT and afternoon DIT was higher than night DIT, suggesting that the time when a meal is consumed affects the thermogenic response and must be considered in the energy balance (40).

In addition to the timing, our findings demonstrate that the same caloric intake throughout the day for a period of 12 weeks leads to a different final body weight and glycemic response. This concept is novel, as dietary interventions nowadays take into account only total daily energy intake rather than the timing of food consumption. The importance of the timing with the same caloric intake has recently been shown in mice, as a 4-h window of high-fat diet, which led to a similar caloric intake as whole day low-fat diet intake, resulted in decreased body weight and improved metabolism (25). To the best of our knowledge, this is the first prospective study that examined the association between the metabolic syndrome and nutrient timing throughout the day, as opposed to focusing on breakfast or night meals only. Moreover, we adjusted for total daily and meal energy intake, which indicates that nutrient timing influences metabolic parameters independently of total daily energy intake. Thus, the difference in weight loss between the BF and D groups could be because of the differences in energetic efficiency.

Although meal size has crucial implications on weight gain, appetite, and glucose and lipid metabolism (18), combined timing and portion size has not been demonstrated. The strength of the present study is that it was conducted in a free-living population, so that the results can be easily translated to obese and overweight persons seeking to lose weight. However, the limitation of the study is that supervision could not be as strict as being under laboratory conditions and some behavioral and diet changes could not be controlled. The present study was also for a short period of time, which diminishes the power to detect follow-up differences between the groups. It is clear that future studies examining larger cohorts for longer periods of time are necessary to determine the long-term benefits of increased caloric content during breakfast vs. dinner for weight loss.

In summary, our results demonstrate that high-calorie breakfast shows increased compliance and is more beneficial than high-calorie dinner for weight loss, insulin sensitivity, and hunger suppression. Our study indicates that avoidance of large meals in the evening may be particularly beneficial in improving glucose and lipid profiles and may lead to reduced risk of type 2 diabetes and cardiovascular diseases. Thus, in people affected by the metabolic syndrome, dietary recommendations aimed at weight reduction and prevention of high postprandial insulin excursions should include advice on time-of-day of nutrient intake in addition to the overall food intake. However, the long-term potential health benefits of high energy intake in the morning need to be assessed. O

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