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ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 1729–1734
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Impact of reduced meal frequency without caloric restriction on glucose regulation in healthy, normal-weight middle-aged men and women

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Received 16 May 2007; accepted 3 July 2007

Abstract

An unresolved issue in the field of diet and health is if and how changes in meal frequency affect energy metabolism in humans. We therefore evaluated the influence of reduced meal frequency without a reduction in energy intake on glucose metabolism in normal-weight, healthy male and female subjects. The study was a randomized crossover design, with two 8-week treatment periods (with an intervening 11-week off-diet period) in which subjects consumed all of their calories for weight maintenance distributed in either 3 meals or 1 meal per day (consumed between 4:00 PM and 8:00 PM). Energy metabolism was evaluated at designated time points throughout the study by performing morning oral glucose tolerance tests and measuring levels of glucose, insulin, glucagon, leptin, ghrelin, adiponectin, resistin, and brain-derived neurotrophic factor (BDNF). Subjects consuming 1 meal per day exhibited higher morning fasting plasma glucose levels, greater and more sustained elevations of plasma glucose concentrations, and a delayed insulin response in the oral glucose tolerance test compared with subjects consuming 3 meals per day. Levels of ghrelin were elevated in response to the 1-meal-per-day regimen. Fasting levels of insulin, leptin, ghrelin, adiponectin, resistin, and BDNF were not significantly affected by meal frequency. Subjects consuming a single large daily meal exhibit elevated fasting glucose levels and impaired morning glucose tolerance associated with a delayed insulin response during a 2-month diet period compared with those consuming 3 meals per day. The impaired glucose tolerance was reversible and was not associated with alterations in the levels of adipokines or BDNF.

1. Introduction

Glucose intolerance and insulin resistance are prominent features of type 2 diabetes mellitus [1]; and a more subtle impairment of glucose tolerance may increase the risk of diabetes, cardiovascular disease, and stroke [2,3]. Such "prediabetic" states in otherwise healthy individuals are characterized by modest elevations of fasting plasma glucose and insulin levels and altered temporal profiles of plasma glucose and insulin levels in the oral glucose tolerance test (OGTT), with greater and more sustained elevations of glucose levels and a delayed insulin response [4-6]. Reduced insulin sensitivity of skeletal muscle cells and decreased responsiveness of pancreatic β-cells contribute to impaired glucose tolerance [7].

Adipokines are hormones produced by fat cells in response to feeding or fasting that may play important roles in the development of obesity and diabetes [1]. For example, levels of circulating leptin are increased in obese and diabetic individuals; and leptin resistance in hypothalamic cells that normally suppress food intake likely

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0026-0495/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2007.07.018

contributes to overeating in these conditions [8,9]. Levels of circulating adiponectin are low and levels of resistin are elevated in obese and insulin-resistant individuals [10]. However, the roles of alterations in adipokines in impaired glucose metabolism are unclear. In addition to insulin and adipokines, brain-derived neurotrophic factor (BDNF) has recently been suggested to play a role in glucose metabolism. Studies of BDNF heterozygous knockout mice [11], obese and diabetic animals administered BDNF [12,13], and humans with type 2 diabetes mellitus [14] suggest that BDNF signaling enhances insulin sensitivity. An antidiabetic action of BDNF in humans is suggested by a recent study that demonstrated an inverse association between fasting plasma BDNF levels and glucose levels, but not insulin levels [14]. However, the effects of variations in dietary energy intake on BDNF levels in humans are unknown.

Intermittent fasts over periods of days have been shown to improve glucose tolerance in obese subjects [15]. Similarly, intermittent feeding and fasting reduce diabetes incidence in rats [16]. Alternate-day fasting (a 24-hour fast every other day) improves glucose regulation and indicators of cardiovascular health in mice and rats [17-19]. On the other hand, several epidemiological studies and short-term (days) intervention experiments have suggested an association between meal skipping (particularly breakfast) and poor health [20-22]. There is therefore a need for controlled studies that directly compare the effects of different meal frequencies on human health [23], a gap in knowledge identified by the 2005 Dietary Guidelines Advisory Committee Report as a future research direction [24]. Intermittent fasting usually results in an overall reduction in calorie intake in animals [25] and humans [26], raising the question of whether the effects of such diets are the result of caloric restriction rather than fasting. In addition, most studies of dietary energy restriction have been performed on overweight and/or diabetic human or animal subjects. In recent studies, nonobese subjects had an overall reduction in energy intake and lost weight when maintained on an alternate-day calorie restriction (CR) regimen [27,28]. We therefore performed a study to determine the effects of reduced meal frequency (1 meal per day) without caloric restriction on health indicators in normal-weight middle-aged male and female subjects.

2. Subjects and methods

2.1. Subjects and study design

Details of the subject characteristics and study design have been reported previously [29]. Briefly, the subjects were healthy 40- to 50-year-old men and women with body mass indexes between 18 and 25 kg/m^2 and with a usual eating pattern of 3 meals per day. Study entry was approved by a physician based on medical history, screening blood and urine test results, and a physical examination. The protocol was approved by the Johns Hopkins University Committee on Human Research and the MedStar Research Institute Institutional Review Board. All subjects gave their informed consent and were compensated for their participation in the study. Each subject underwent two 8-week controlled-diet periods during which they consumed all of their calories for weight maintenance in either 3 meals per day (breakfast, lunch, and dinner) or 1 meal per day (during a 4-hour period in the early evening; 4:00 to 8:00 PM) in a randomized crossover design with an 11-week off-diet period between the 2 controlled-diet periods. In the experimental diet, breakfast and lunch food items were substituted for traditional evening meal items; the composition of the diets was reported previously [28]. Energy intake was adjusted as necessary to maintain constant body weight during the study.

2.2. Glucose tolerance test and measurements of hormone levels

These methods have been described previously [30]. Briefly, all subjects fasted overnight (no food or caloric beverages after 8:00 PM) before the OGTT; and an initial blood sample was obtained for measurements of fasting glucose, insulin, leptin, ghrelin, adiponectin, resistin, and BDNF. The subjects then drank 75 g of glucose in a 300-mL solution (SunDex; Fisherbrand, Pittsburgh, PA); and additional blood samples were obtained at 5, 10, 15, 20, 40, 60, 80, 100, and 120 minutes for plasma glucose and insulin measurements. Plasma glucose concentrations were measured using a glucose analyzer (Beckman Instruments, Brea, CA). Plasma insulin and resistin concentrations were measured using enzyme-linked immunosorbent assays (ELISA) (Alpco Diagnostics, Salem, NH) with intraassay variations of 4.8% to 9.0% and 2.8% to 3.4% and interassay variations of 2.6% to 3.6% and 5.1% to 6.9%, respectively. Plasma leptin levels were measured using ELISA (LINCO Research, St Charles, MO) with intraassay variations of 1.09% to 4.98% and interassay variations of 3.89% to 5.33%. Plasma adiponectin levels were measured by radioimmunoassay (LINCO) having an intraassay and interassay variation of 1.78% to 6.21% and 6.9% to 9.25%, respectively. Plasma ghrelin levels were measured by radioimmunoassay (Phoenix Pharmaceuticals, Belmont, CA) with calculated intraassay and interassay variations of 6.7% and 7.8%, respectively. Plasma BDNF levels were measured by ELISA (Promega, Madison, WI) with range of sensitivity from 7.8 to 500 pg/mL and with interassay variation measured at 8.8% (low concentration), 2.9% (medium concentration), and 2.2% (high concentration).

2.3. Calculation of insulin sensitivity

We quantified insulin sensitivity by calculating the homeostatic model assessment of insulin resistance (HOMA-IR) using fasting plasma glucose and insulin levels [31]. We also calculated the insulin sensitivity index (ISI), metabolic clearance rates (MCR), β-cell function during first phase secretion (β-cell function, first phase) and second

Table 1
Biomarkers in subjects when consuming either 1 meal per day or 3 meals per day

	1 meal	3 meals	P [a]
Glucose (mg/dL)	95.9 ± 1.7	85.4 ± 1.7	.0002
Insulin (μU/mL)	5.0 ± 0.7	5.8 ± 0.7	.4329
Glucagon (pg/mL)	66.5 ± 7.7	62.1 ± 7.4	.6878
HOMA-IR	1.2 ± 0.2	1.3 ± 0.2	.8718
OGIS	403.4 ± 14.0	458.8 ± 13.9	.0114
ISI	0.1 ± 0.004	0.1 ± 0.004	.6552
MCR	8.8 ± 0.3	9.2 ± 0.3	.4011
β-Cell function 1st phase	782.1 ± 66.0	1013.85 ± 66.1	.0209
β-Cell function 2nd phase	239.0 ± 19.0	253.7 ± 19.0	.5894
Adiponectin (pg/mL)	13.5 ± 1.3	13.5 ± 1.3	.9919
Resistin (ng/mL)	3.1 ± 0.3	2.8 ± 0.2	.4147
Leptin (ng/mL)	20.2 ± 2.2	16.1 ± 2.1	.18
Ghrelin (pg/mL)	163.2 ± 12.8	158.4 ± 12.8	.7942
BDNF (ng/mL)	141.7 ± 26.7	148.1 ± 26.6	.8175

Data are presented as least squares means ± SEM, n = 15 (10 women, 5 men).
[a] P value for the comparison of 1 meal vs 3 meals.

phase secretion (β-cell function, second phase), as well as oral glucose–insulin sensitivity (OGIS; 0, 90 [mean of the 80- and 100-minute values], and 120) [32-35].

2.4. Statistical analysis

A repeated-measures analysis of variance (ANOVA) appropriate for a 2-period, 2-treatment crossover study, where period was considered a repeated measure, was used to evaluate the effects of meal frequency when observations were measured before the start of each treatment period (baseline) and at the end of the treatment period (the MIXED procedure in SAS, version 9, SAS, Cary, NC). Sequence, treatment, and period were included in the model as fixed effects. Subject within sequence was included as a random effect. Period-specific baseline values were included as a covariate. When multiple measurements were made during a treatment period (ie, glucose at 0, 20, 40, 60, 80, 100, and 120 minutes), a similar statistical model was used to evaluate the effects of meal frequency, including time as an additional repeated-measures variable. Observation time and the interaction between time and treatment were included as fixed effects in the model. Where the interaction between time and treatment was statistically significant ($P < .05$), within-time treatment effects were evaluated. Data are presented as least squares means and SEMs.

3. Results

Morning plasma glucose concentrations were significantly greater in subjects when they were consuming 1 meal per day compared with when they were consuming 3 meals per day (Table 1). When consuming 1 meal per day, the subjects exhibited poorer glucose tolerance as indicated by a significantly greater and more prolonged elevation of plasma glucose concentrations compared with subjects consuming 3 meals per day (Fig. 1). Fasting plasma insulin concentrations were not significantly affected by meal frequency (Table 1); and there were no significant effects of diet on insulin responses to glucose during the OGTT, although there was a trend toward a delayed insulin response when subjects consumed 1 meal per day (Fig. 2).

There were no significant effects of meal frequency on HOMA-IR, ISI, or MCR (Table 1). However, the OGIS values were significantly lower in subjects when on 1 meal per day compared with 3 meals per day (Table 1). In addition, when on 1 meal per day, the values for the first phase of β-cell function were significantly lower than the value when on 3 meals per day (Table 1). Values for the

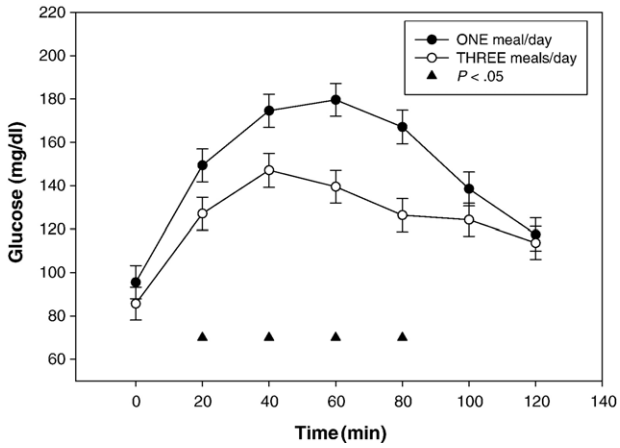

Fig. 1. Plasma glucose concentrations during the OGTTs during each study period. Data are presented as least squares means ± SEM, n = 15 (10 women, 5 men), from a repeated-measures ANOVA. There was a significant treatment effect between 1 meal per day (●) and 3 meals per day (○) for the OGTT at 20, 40, 60, and 80 minutes; ▲$P < .05$.

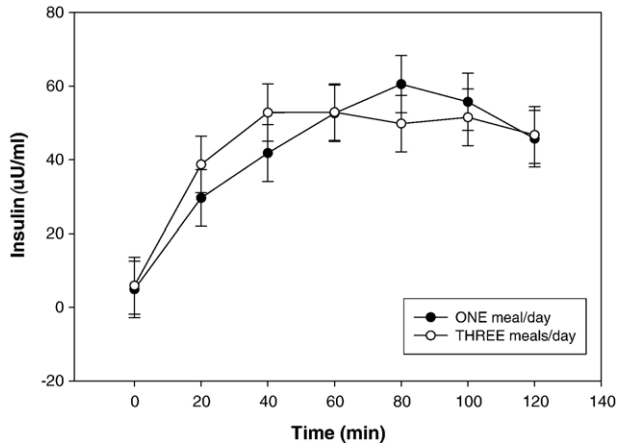

Fig. 2. Plasma insulin concentrations during the OGTTs during each study period. Data are presented as least squares means ± SEM, n = 15 (10 women, 5 men), from a repeated-measures ANOVA. There was no significant treatment effect between 1 meal per day (●) and 3 meals per day (○) for plasma insulin concentrations during the OGTT.

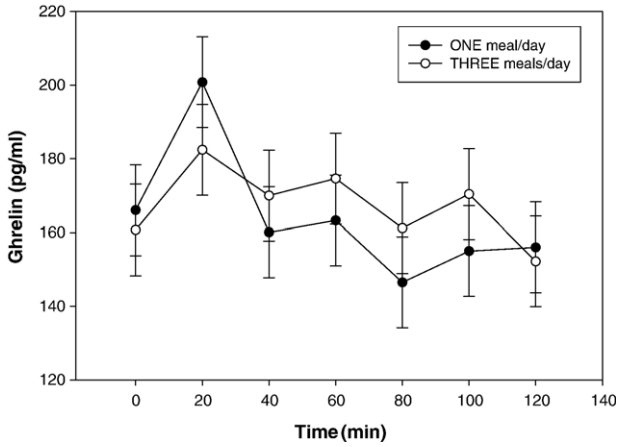

Fig. 3. Plasma ghrelin concentrations during the OGTTs during each study period. Data are presented as least squares means ± SEM, n = 15 (10 women, 5 men), from a repeated-measures ANOVA. There was no significant treatment effect between 1 meal per day (●) and 3 meals per day (○) for plasma ghrelin concentrations during the OGTT.

second phase of β-cell function were not significantly affected by diet.

To further elucidate the effects of meal frequency without caloric restriction on energy metabolism, we measured fasting levels of several adipokines that are known to play important roles in regulating energy balance. The fasting plasma ghrelin concentration was similar in subjects when on 1 meal per day or 3 meals per day (Table 1). There were no significant effects of diet on plasma ghrelin concentrations during the OGTT, although levels tended to be lower in subjects when on 1 meal per day for time points between 40 and 100 minutes after the glucose ingestion (Fig. 3). Diet had no significant effects on morning plasma concentrations of glucagon, leptin, adiponectin, resistin, and BDNF (Table 1).

4. Discussion

This controlled randomized dietary intervention study is among the first to evaluate the effects of meal frequency on glucose regulation in normal-weight, middle-aged men and women. Each subject consumed the same amount of calories each day regardless of whether they ate 1 or 3 meals, and all subjects maintained their body weight within 2 kg of their initial weight throughout the 6-month period [29]. Most physiological variables measured, including heart rate, body temperature, and blood chemicals, were unaffected by meal frequency; however, when on 1 meal per day, subjects exhibited a significant reduction of fat mass and significant increases in levels of total, low-density lipoprotein, and high-density lipoprotein cholesterol [29]. In the present study, morning glucose tolerance was impaired when subjects were consuming 1 meal per day compared with 3 meals per day. Fasting (morning) plasma glucose levels were significantly elevated in subjects when they were consuming 1 meal per day compared with 3 meals per day. The latter difference in fasting glucose levels could be explained, in part, by continuing absorption of the greater amount of food consumed in the evening in the subjects on the 1-meal-per-day diet. Other studies have suggested an adverse effect of meal-skipping diets on insulin sensitivity [20-22]; however, these studies were either epidemiological (with inherent confounds) or involved very short-term (days) changes in diet. Whether the effect of the 1-meal-per-day diet on glucose tolerance would persist, exacerbate, or resolve over time beyond the 2-month experimental diet period of our study is an important question relevant to long-term effects of the diet. However, we did find that the effect of the 1-meal-per-day diet on glucose tolerance was rapidly reversed upon return to the 3-meals-per-day diet, indicating that the diet had no long-lasting effect on glucose metabolism.

The cause of the impaired morning glucose tolerance in subjects consuming 1 meal per day compared with 3 meals per day is unclear. Fasting insulin, leptin, and glucagon concentrations have been reported to be elevated in subjects with impaired glucose tolerance [36,37]. However, there were no significant effects of diet on concentrations of the latter hormones in the present study. Similarly, there were no significant effects of meal frequency on plasma levels of ghrelin, adiponectin, resistin, or BDNF. Thus, although fasting insulin and adipokine levels were not different between the 2 diet groups, insulin sensitivity was apparently decreased in subjects when consuming 1 meal per day. Indeed, the values for OGIS and first phase β-cell function were significantly lower in the subjects when they were consuming 1 meal per day compared with baseline, 3-meals-per-day, and off-diet values. The latter results suggest a relative impairment of insulin sensitivity and pancreatic β-cell insulin responses in subjects on 1 meal per day compared with 3 meals per day.

The OGTTs were performed in the morning. Therefore, when on the 1-meal-per-day diet, the subjects had consumed a much greater amount of food in proximity to the OGTT compared with subjects on 3 meals per day, which could have influenced morning insulin sensitivity. Moreover, circadian variations in glucose tolerance have been documented, with tolerance being best in the morning [38]. When not accustomed to a morning meal and then subjected to a morning OGTT, the subjects eating 1 meal per day may therefore exhibit poorer glucose tolerance compared with those adapted to eating breakfast. However, the current manner of eating by Westernized society of consuming the largest meal in the evening would appear to be a maladaptive lifestyle.

Our findings show that consumption of one unusually large meal per day worsens morning glucose tolerance compared with an isocaloric diet spread across 3 meals. However, when on 1 meal per day, the subjects would have eaten less than those on 3 meals per day if we had not asked them to consume the same amount of food that they normally eat on a 3-meals-per-day schedule. When rodents are subjected to an alternate-day fasting regimen, their overall

calorie intake is decreased by 10% to 30%, they maintain a lower body weight than animals on an ad libitum control diet, and they exhibit increased insulin sensitivity and decreased blood pressure [11,25]. Similarly, when maintained on an alternate-day CR diet over a 2-month period, human subjects lost weight and exhibited improved cardiovascular disease and diabetes risk profiles [28]. In the latter study, the subjects ate only 400 to 500 cal on CR days, which resulted in a reduction in plasma leptin levels and an elevation of β-hydroxybutyrate levels only on the CR days, but sustained decreases in plasma insulin levels, suggesting improved insulin sensitivity. Collectively, the available data therefore suggest that meal skipping or intermittent CR diets can result in health benefits including improved glucose regulation, but only if there is an overall reduction in energy intake.

Acknowledgments

This research was supported by the Intramural Research Program of the National Institute on Aging. We thank K Spears for technical assistance.

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