Kinetic Analysis of the Thermic Effect of Food and Its Relationship to Body Composition in Humans

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The course of energy expenditure after a meal can vary widely with regard to the slope of onset, amplitude, and duration of the thermic effect. The aim of the present study was to explore the relationship between the thermic effect of food (TEF), as characterized by kinetic analysis of postprandial energy expenditure, body composition, and variables related to the metabolic syndrome including central obesity, hypertension, and glucose tolerance. A total of 181 men and women (body mass index [BMI] range, 19.4 to 52.2 kg/m^2) were characterized for body composition, blood pressure, oral glucose tolerance, and energy expenditure after a test meal. Energy expenditure, as measured by indirect calorimetry, was analyzed over a 6-hour period by 3-parameter curve fitting using equations derived from kinetics describing a biphasic reaction involving 2 consecutive first-order reactions (A → B → C). Apart from total thermic effect of food (TEF_k), the curve also provided an estimate of time of peak (T_p) and amplitude of peak (A_p) for each subject. Multiple stepwise regression analysis with TEF_k, A_p, and T_p as dependent variables showed significant effects of sex, age, body weight, body fat, β-blockade, and body composition on TEF curve parameters. Cluster analysis based on T_p shown 2 distinct clusters with significant differences in age and body fat mass. This study shows that kinetic analysis of postprandial energy expenditure can be used to examine the determinants of the time course of the thermic effect of food in man.

TOTAL ENERGY EXPENDITURE (TEE) can be divided into several distinct components that may each contribute to long-term alterations in energy homeostasis and thus body composition. Although the thermic effect of food (TEF) only accounts for a relatively small proportion of daily energy expenditure (3% to 10%), small differences in TEF over long periods of time may significantly contribute to the development and/or maintenance of obesity.[1,2] As recently reviewed by deJonge and Bray,[3] several factors, including insulin resistance, sympathetic activity, and body fat may have an important influence on TEF.

As pointed out by Reed and Hill,[4] many of the discrepant findings reported in this field may be attributed to methodological differences in the assessment of TEF. Thus, most investigators have expressed TEF simply as the area under the curve (AUC) after a test meal. However, it is now clear that the course of energy production after a meal can vary widely with regard to the slope of onset, amplitude, and duration of the thermic effect. Reed and Hill[4] have shown that the time course of the thermic response to food can be described with the help of a 3-parameter curve fitting. Based on their exploration of the thermic response to food with this approach, they proposed that the time course of the thermic response may differ between lean and obese individuals and may well contribute to differences in energy balance, despite a similar AUC.

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The aim of the present study was to explore the relationship between the thermic effect of food, as characterized by kinetic analysis of postprandial energy expenditure, body composition, and variables related to the metabolic syndrome including central obesity, hypertension, and glucose tolerance.

SUBJECTS AND METHODS

Subjects

One hundred and eighty-one men (n = 54) and women (n = 127) with a wide range of body weight (body mass index [BMI] range, 19.4 to 52.2 kg/m^2), with and without hypertension, volunteered for the study. Patients with diabetes mellitus, congestive heart failure, abnormal renal or liver function, and intentional weight reduction during the last 3 months were excluded from the study. Obesity was defined as a BMI $\geq$ 30 kg/m^2, and central obesity was defined in women as waist-to-hip ratio (WHR) greater than 0.85, and in men as WHR greater than 1.0.[5] Hypertension was defined as a 24-hour ambulatory blood pressure level greater than 135/85 mm Hg (90207, SpaceLabs Medical Inc, Redmond, WA)[6] and/or the intake of antihypertensive medication. Patients were also assessed for the intake of thyroid hormone and other medication. The study protocol was approved by the institutional Ethics Committee, and all subjects gave informed consent before participating in the study.

Study Protocol and Methods

All subjects were characterized for weight, height, and waist and hip circumference, and body composition was determined by bioelectrical impedance analysis (AKERN-RJL BIA 101/S, Frankfurt, Germany).[7] After a 60-minute resting period after insertion of a venous cannula, fasting blood samples were collected for the measurements of glucose, insulin, epinephrine, and norepinephrine. An oral glucose tolerance test (75 g glucose in 250 mL water) was then performed with collection of blood samples for insulin and glucose measurements at 60 and 120 minutes.[8]

For the measurement of energy expenditure, subjects were admitted on the evening before the test to a metabolic ward, where they were given a light evening snack. After a 12-hour overnight fast, resting metabolic rate was measured in the sitting subject in a temperature-controlled room over 2 25-minute periods extending over 2 hours, with an open-circuit indirect calorimetry system (standardized for temperature, pressure, and moisture) fitted with a face mask (Sensor Medics 2900 Z, NewMedics Medizinelektronik, Öhringen, Germany). After

baseline measurements, subjects consumed a test meal consisting of curds (350 g containing 1 MJ, 12.1% protein, 4.6% carbohydrate) within 10 minutes. The rationale for selecting a high protein diet (0.8 MJ from protein) was based on the fact that protein is known to elicit the largest thermogenic response. Energy expenditure was then measured for 25 minutes every hour for the next 6 hours, during which the subject remained awake and seated. Complete urine samples were collected separately during 2 hours before and 6 hours after the test meal. The calorimetry system was recalibrated several times during the day using a reference gas mixture. For each measurement, the first 5 minutes were discarded to allow subjects to adapt to the measurements procedure, and the data from the remaining 20 minutes were averaged and used to calculate energy expenditure from the oxygen consumption, carbon dioxide production, and urinary nitrogen excretion.[9,10]

Analytical Methods

Plasma glucose was measured by a glucose analyzer (Beckman Instruments, Munich, Germany), plasma epinephrine and norepinephrine by high-performance liquid chromatography with electrochemical detection,[11] and plasma insulin by radioimmunoassay (Biermann, Bad Nauheim, Germany). AUC was calculated for glucose and insulin response during oral glucose tolerance test (OGTT) by the trapezoidal rule.

Kinetic Analysis of the Thermic Effect of Food

The TEF was calculated as the area under the response curve minus resting metabolic rate (RMR) (extrapolated from the average value of baseline measurements to the end of the meal) using 2 different approaches: conventional TEF_a was calculated as AUC of energy expenditure after the test meal minus the 6-hour RMR by the trapezoidal rule; in contrast, TEF_k was calculated as AUC from a 3-parameter curve fit describing the TEF curve until baseline was achieved using the following equation 1:

$$\Delta y = a\frac{b}{c-b}(c^{-bx} - e^{-cx}) \quad (1)$$

This equation is derived from kinetics describing a biphasic reaction involving 2 consecutive first-order reactions (A → B → C). The kinetics data were analyzed to obtain 2 rate constants and the molar absorptivity of the intermediate species B. The coefficient a is the initial concentration of the reactant species and b and c are the rate constants.[12] X stands for the time in hours.

To determine the AUC, the above equation was integrated to equation (2) and the peak time was derived by equation (3).

$$\int \Delta y = \frac{ac - ab}{c^2 - bc} \quad (2)$$

$$f'(x) = \frac{\ln\frac{b}{c}}{b - c} \quad (3)$$

Nonlinear least-squares curve fit analysis was performed using a solver integrated in Excel 5.0 (Microsoft, Redmond, WA). The solver is an optimization routine that finds the maximum, minimum, or specified value of a target cell by varying the values in 1 or several cells. After finding the set of least-squares regression coefficients, the standard deviations of the coefficients and the correlation coefficient (R^2) were calculated using a macro to provide regression statistics for the solver.[12] An $R^2 \geq 0.6$ was defined as the minimum criterium for the solver statistics.

An example of the curve fit based on the actual TEF data of 1 proband is shown in Fig 1. A similar curve fit with determination of TEF_k, time of peak (T_p), and amplitude of peak (A_p) was performed for each subject.

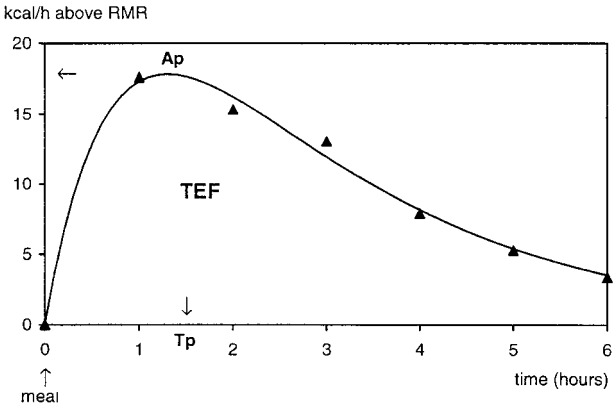

Fig 1. Example of one subject's actual TEF data (L) and the corresponding TEF curve fit: equation of the TEF curve: 31.42* 1.2* [exp (−1.24*x) − exp (−0.43*x)]/(0.43 − 1.24). a = 31.41 kcal/min; b = 1.24 1/h; c = 0.43 1/h; T_p = 1.30 hours; A_p = 17.9 kcal/h (74.9 kJ/h); TEF = 73 kcal (303 kJ); R^2 = .99; $\sqrt{}$SE = 0.67. The arrow indicates the end of the meal.

Statistical Analysis

Statistical analysis was performed using the SPSS-PC+ software package (SPSS Inc, Chicago, IL). Data are reported as means ± standard deviation (SD). Differences and correlations were considered significant at $P < .05$.

Differences between groups were tested for significance by 2-tailed Student's *t* test for independent samples or the nonparametric Mann-Whitney *U* test as appropriate. χ^2 statistics were used to detect differences in the distribution of men and women, obesity, central obesity, impaired glucose tolerance, hypertension, and β-adrenergic blockade or thyroid medication between groups. The associations between the parameters of the TEF curve fitting, anthropometric measurements, and age were obtained using Pearson correlation coefficients after establishing that the data were normally distributed. For parameters not normally distributed (fat-free mass [FFM] [kg], TEF_k [kJ]) nonparametric Spearman correlation coefficients were calculated. Stepwise multiple linear regression analysis with TEF_k curve parameters as dependent variables were performed to explore the dependence of variables such as sex, age, body weight, body composition, WHR, hypertension, impaired glucose tolerance, epinephrine, norepinephrine, obesity, central obesity, drugs, and thyroid hormones. Analysis of covariance (ANCOVA) for independent samples was used to compare the relationship between the amplitude of peak and body composition, controlling for sex. As TEF_k was not normally distributed, this variable was transformed to a natural logarithm to approximate normal distribution for performing regression analysis as dependent variable. Clusters were determined by hierarchical cluster analysis (complete linkage, squared euclidic distance) based on T_p.

RESULTS

Curve-Fit Analysis

Based on the predefined criterium of an $R^2 \geq 0.6$ required for solver statistics, only 166 of the studied subjects (91.7%) were included in the final evaluation. There was, however, no significant difference between the male/female ratio (20/80% *v* 31/69), age (56 *v* 52 yr), BMI (30.6 *v* 31.4 kg/m^2), percentage body fat (28.8% *v* 29.2%), and percentage hypertensives (67% *v*

69%) between the 15 subjects who were excluded from analysis and the remaining group. Characteristics of the remaining subjects are presented in Table 1.

TEF_a based on energy expenditure calculated as AUC within 6 hours was significantly correlated with TEF_k as determined by the curve fit analysis ($r = .92$, $P < .0001$; Fig 2). A multiple stepwise regression analysis with TEF_k (transformed to ln-TEF_k), A_p, and T_p as dependent variables showed significant effects of sex, age, body weight, body fat, β-blockade, and body composition on TEF curve parameters. Body weight determined 5.4% of ln TEF_k ($P \leq .007$, $\sqrt{SE} = 0.36$ ln (kJ)). β-adrenergic blockade and age together explained 8.8% of T_p ($P \leq .001$, $\sqrt{SE} = 0.47$ hour). ANCOVA for independent samples, with A_p as dependent variable controlling for sex, showed that body fat mass was the best predictor of A_p. Together, fat mass and sex explained 14.9% of A_p ($P \leq .0001$). Age, body weight, and body composition were also significantly correlated to TEF_k, T_p, and A_p (Table 2). In contrast, hypertension, impaired glucose tolerance, catecholamines, and thyroid hormone medication had no effect on the TEF-curve parameters. The components influencing the shape of the TEF curve are summarized in Fig 3. Higher body weight and body fat increased TEF_k and A_p independently of sex. Higher relative body-FFM was associated with a faster peak, whereas greater relative body fat mass, β-blockade, and aging delayed T_p.

Cluster Analysis

As there was a significant difference in A_p between men and women (1.39 ± 0.35 *v* 1.16 ± 0.30 kJ/min; $P < .0001$), hierarchical cluster analysis was based on T_p. This showed 2 distinct clusters characterized by differences both in A_p and T_p (Fig 4). Table 3 summarizes the characteristics of the subjects in both clusters. Postprandial energy expenditure 1 hour after the test meal was significantly higher in cluster 1 (CLU1) than in cluster 2 (CLU2) (347.7 ± 57.6 kJ/h *v* 307.6 ± 57.1 kJ/h; $P \leq .005$), whereas resting and diet-induced metabolic rate at the other time points were not different. Comparisons between the 2 clusters regarding coefficients a, b, and c showed significantly higher rate constants in CLU1 (b: 1.85 ± 3.10 1/h; c: 0.56 ± 0.25 1/h) than in CLU2 (b: 0.56 ± 0.23 1/h; c: 0.40 ± 0.12 1/h, $P < .05$), indicating a slower time course of the thermic response in CLU2. TEF_k in subjects in CLU2 was 27% higher ($P < .005$) than in subjects in CLU1 (Table 3). Subjects in CLU2 were older and had a higher relative body fat mass ($P < .05$) despite similar body weight and BMI. While the frequency of hypertension was similar between the 2 clusters, patients in CLU2 were more often on β-blockers ($P < .05$). Nevertheless, a subset analysis excluding patients with β-adrenergic blockade showed significantly higher body-fat mass (37.3% ± 5.8% *v* 31.7% ± 8.4%; $P < .05$) with no difference in BMI and body weight between CLU1 (n = 112) and CLU2 (n = 13).

Table 1. Characteristics of the 166 Subjects

	Mean ± SD	Range
Age (yr)	52.3 ± 10.8	(19.0-74.0)
Height (cm)	167.2 ± 9.5	(148.0-193.0)
Body weight (kg)	87.8 ± 18.0	(50.5-146.2)
BMI (kg/m²)	31.4 ± 6.1	(19.4-52.2)
Body FFM (kg)	58.4 ± 12.4	(36.2-94.4)
Body fat mass (kg)	29.2 ± 10.5	(9.7-69.6)
Body FFM (%)	67.1 ± 8.0	(52.4-85.3)
Body fat (%)	32.8 ± 7.9	(14.7-47.6)
WHR (F)	0.90 ± 0.05	(0.76-1.04)
WHR (M)	0.98 ± 0.04	(0.85-1.09)
Female/male (%)	69/31	
Obese subjects (%)	54.8	
Subjects with central obesity (%)	68.7	
Subjects with hypertension (%)	69.9	
Treated hypertension (%)*	83.6	
With β-blockade (%)†	42.2	
With diuretics (%)†	28.9	
With CCB, ACEI, others (%)†	28.9	
Subjects treated with thyroid hormones (%)	13.9	
Subjects with IGT (%)	47.0	

Abbreviations: WHR, waist-to-hip ratio; CCB, calcium channel blockade; ACEI, angiotensin converting enzyme inhibitors; IGT, impaired glucose tolerance.

*Percent of subjects with hypertension.

†Percent of subjects with treated hypertension.

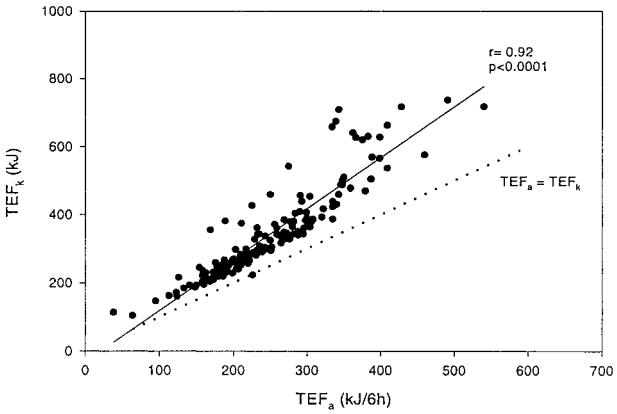

Fig 2. Regression line for TEF_a calculated as AUC of energy expenditure after the test meal minus the 6-hour RMR compared with TEF_k calculated as a three-parameter curve fit. Regression line: y = −31.0 + 1.5*x ($R^2 = .85$). Dotted line: $TEF_a = TEF_k$.

DISCUSSION

Kinetic analysis of TEF, using the above equations, was performed with a reasonable fit in 91.7% of the subjects, indicating that these equations represent a good model for describing the thermic response to a meal. Although there was a significant correlation between TEF_k and the conventional TEF_a (based on AUC), TEF_k was approximately 50% higher than TEF_a. This is most likely attributable to the fact that, as demonstrated by previous investigators,[4,13,14] the TEF, depending on composition and size of a meal,[14-16] does not return to baseline for as long as 5 to 6 hours. This is the case particularly with a high-protein meal as used in our study, which is known to elicit a longer and greater thermogenic response than a high-carbohydrate or high-fat diet.[3] From our comparison, it appears that this extended thermic response is more likely to be resolved

Table 2. Pearson and Spearman Correlation Coefficients for the Relationship Between Subjects' Characteristics and the TEF_k, the A_p, and the T_p

	FFM (kg)	FM (kg)	FFM (%)	FM (%)	Age (y)	TEF_k (kJ)	A_p (kJ/min)	T_p (hour)
BW (kg)	0.84*	0.74*	−0.24†	0.24†	−0.001	0.21†	0.27‡	−0.09
FFM (kg)	—	0.23†	0.25†	−0.26‡	−0.08	0.16†	0.35*	−0.19†
FM (kg)		—	−0.82*	0.82*	0.07	0.15	0.07	0.07
FFM (%)			—	−0.99*	−0.16†	−0.06	0.13	−0.16†
FM (%)				—	0.15	0.07	−0.13	0.16†
Age (yr)					—	0.04	−0.10	0.19†
TEF_k (kJ)						—	0.64*	0.26‡
A_p (kJ/min)							—	−0.39*

NOTE. Nonparametric Spearman's correlation coefficients for all relationships with FFM (kg) and TEF_k (kJ).
Abbreviations: BW, body weight; FFM, body fat-free mass; FM, body fat mass.
*$P \leq .0001$.
†$P \leq .05$.
‡$P \leq .001$.

by kinetic analysis than by the conventional analysis, as the 3-parameter curve fit extrapolates the AUC until energy expenditure returns to baseline and thus provides an estimate of unmeasured TEF. This is also well in line with the previous report by Segal et al,[17] suggesting that a 3-hour measurement of TEF, while perhaps sufficient for a rough comparison between subjects, may only represent 60% to 70% of total TEF. As indicated by our results, given the differences in T_p between individuals, there is clearly important information in the remaining TEF beyond 3 hours that can be determined by kinetic analysis. We, therefore, agree with Reed and Hill,[4] who point out that the shorter the duration of measurement, the more likely it is that the total TEF will differ between groups.[18] In fact, these investigators have previously suggested the use of a three-parameter curve fit to determine the kinetics of the TEF. In our study, we now show that this approach, albeit with our equations, does indeed allow description of the TEF in the vast majority of probands over a wide range of age, body composition, and other variables known to effect the thermic response.

Apart from a more complete assessment of the magnitude of TEF, kinetic analysis also provides important information regarding the time course of the thermic response. Thus, as shown by our data, the T_p and A_p of the thermic response can vary considerably among individuals, so that a delayed T_p can lead to a considerable prolongation of TEF and substantial increase in AUC when extrapolated to baseline. Under normal circumstances, most individuals would not return to baseline before the next meal. Thus, one may speculate that at the time of the following meal, the thermic response in individuals with a delayed T_p and lower A_p will be less than in subjects with an early T_p and high A_p, thereby possibly contributing to a higher positive energy balance and weight gain in the long-term.

Kinetic analysis also showed that there was a disparate effect of various determinants of TEF on different aspects of the thermic-response curve. Thus, while A_p was higher in men than in women, T_p was delayed in older individuals and in patients on β-blockers and was positively related to relative fat mass. These findings are supported by the results of the cluster analysis, which showed 2 distinct patterns: CLU1, with a higher A_p and shorter T_p, and CLU2, with a lower A_p and extended T_p. Patients in CLU1 were younger, had a higher FFM, and were less likely to be on β-blockers than patients in CLU2. In contrast, BMI, body weight, WHR, blood pressure, glucose tolerance, and plasma catecholamines were comparable between the 2 groups. It is thus conceivable that the differences in

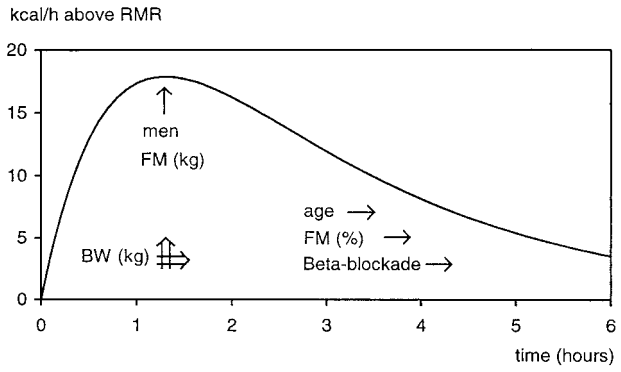

Fig 3. Influence of body composition, age, and β-adrenergic blockade on the TEF curve shifts. ↑ increased A_p, → delayed T_p, ⇳ increased TEF_k.

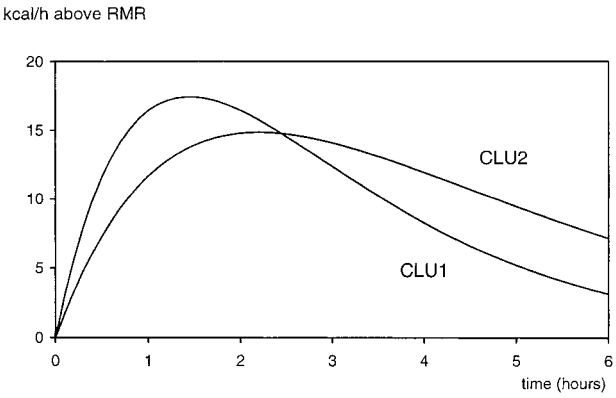

Fig 4. TEF curves from CLU1 and CLU2 calculated with the average values of basal (t = 0 hours) and postprandial energy expenditure (t = 1 to 6 hours)) of CLU1 and CLU2, resulted from hierarchical cluster analysis. Equation for CLU1: 42.1* 0.78* [exp (−0.78*x) − exp (−0.61*x)]/(0.61 − 0.78). a = 42.1 kcal/min; b = 0.78 1/h; c = 0.61 1/h; R^2 = .98; √SE = 0.99. Equation for CLU2: 40.4* 0.45* [exp (−0.45*x) − exp (−0.45*x)]/(0.45 − 0.45). a = 40.4 kcal/h; b = 0.4549 1/h; c = 0.4547 1/h; R^2 = .94; √SE = 1.35.

Table 3. Characteristics of Subjects in CLU1 and CLU2

	CLU1 (n = 143)	CLU2 (n = 23)
Age (yr)	51.6 ± 10.8	56.4 ± 9.9*
BMI (kg/m²)	31.3 ± 6.3	31.9 ± 4.8
Body weight (kg)	87.7 ± 18.0	88.7 ± 18.6
WHR (F)	0.90 ± 0.05	0.90 ± 0.04
WHR (M)	0.98 ± 0.04	1.01 ± 0.05
Body FFM (kg)	58.7 ± 12.6	56.2 ± 10.6
Body fat mass (kg)	28.7 ± 10.4	32.5 ± 10.6
Body FFM (%)	67.6 ± 8.2	63.8 ± 5.4*
Body fat (%)	32.3 ± 8.2	36.2 ± 5.4*
TEF_k (kJ)	324 ± 125	411 ± 153†
A_p (kJ/minute)	1.26 ± 0.33	1.04 ± 0.31†
T_p (hour)	1.30 ± 0.36	2.24 ± 0.44‡
TEF_a	242 ± 80	270 ± 83
Plasma variables		
Epinephrine (ng/L)	16.2 ± 9.7	13.1 ± 4.8
Norepinephrine (ng/L)	271.4 ± 116.3	307.5 ± 179.4
$Glucose_{baseline}$ (mmol/L)	5.5 (3.8-18.4)	5.9 (4.5-7.5)
$Insulin_{baseline}$ (mU/L)	16.8 (2.3-66.5)	19.7 (4.4-50.9)
$AUC_{glucose}$ (mmol/L/minute)	1,002 (540-3,056)	1,154 (630-1,485)
$AUC_{insulin}$ (mU/L/minute)	10,545 (2,238-45,936)	12,491 (4,215-40,359)
Female/male (%)	68/32	78/22
Obese subjects (%)	53.8	60.9
Subjects with central obesity (%)	67.4	82.6
Subjects with hypertension (%)	69.2	73.9
Subjects with β-blockade (%)	21.7	43.5§
Subjects treated with thyroid hormones (%)	12.6	21.7
Subjects with IGT (%)	46.2	52.2

NOTE. Clusters resulted from hierarchical cluster analysis based on the T_p calculated by kinetic analysis of the TEF_k. Values are Mean ± SD or median (range). TEF_a: calculated as area under the curve (AUC) of energy expenditure after the test meal minus the 6-hour RMR by the trapezoidal rule.

*$P \leq .05$ *v* CLU1.

†$P \leq .005$.

‡$P \leq .0001$.

§$\chi^2 = 5.1$, $P < .05$.

kinetics between the 2 clusters were in part attributable to the shift in the relationship between FFM and fat mass with age, with a tendency for a lower ratio of organ mass: FFM as a possible explanation for the age effect in CLU 2.

Importantly, kinetic analysis of the thermic response curve provides interesting insights regarding the relationship between determinants of TEF and the time course of this effect. Thus, for example, while previous investigators have consistently described a lower TEF in older individuals,[15,19,20] our analysis suggests that the change in TEF with aging is more correctly described as a delay in T_p rather than an overall reduction in TEF. In fact, when extrapolated to baseline, older individuals may, in fact, have a similar or even larger AUC than younger individuals over the entire time course. Similarly, while previous investigators have suggested that the TEF is reduced in patients with insulin resistance,[21,22] our kinetic analysis found no relationship between impaired glucose tolerance and any of the TEF curve parameters after the protein meal. Whether or not insulin resistance affects the kinetics of the TEF curve after a glucose load remains to be determined.

While we used a three-parameter curve fit to describe the kinetics of TEF in our study, we cannot rule out that a more extensive curve fit may more fully describe other aspects of the thermic reaction. However, given the fact that we were able to fit the data to the curve in the vast majority of probands over a wide range of age, body weight and other demographic variables, we believe that a 3-parameter curve is the most likely equation to best characterize the kinetic data in the majority of subjects. This assumption is also supported by the fact that the determinants of the different components of the curve shown by our analysis are largely consistent with our current understanding of the physiology of energy expenditure. It must however be noted, that our findings with a high-protein meal may not reflect the findings under a high-carbohydrate or high-fat meal. Clearly, the effect of dietary composition on the thermokinetic response needs to be addressed in future studies.

In summary, in this report, we describe the use of a 3-parameter curve fit analysis to describe kinetic aspects of the thermic response to a test meal in a wide range of individuals. Our findings suggest that amplitude and duration of this effect are independently determined by various demographic and anthropometric factors. Kinetic analysis of the thermic effect of food can provide further insights into the regulation of energy expenditure in health and disease.

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