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HUM5007, a novel combination of thermogenic compounds, and 3-acetyl-7-oxo-dehydroepiandrosterone: each increases the resting metabolic rate of overweight adults☆

John L. Zenk[a,*], Joy L. Frestedt[a], Michael A. Kuskowski[b]

[a]Department of Clinical Affairs, Minnesota Applied Research Center, Edina, MN 55435, USA
[b]Department of Psychiatry, Geriatric Research Education and Clinical Center, Veterans Administration Medical Center, Minneapolis, MN 55417, USA

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Abstract

This study tested the hypothesis that 3-acetyl-7-oxo-dehydroepiandrosterone alone (7-Keto) and in combination with calcium citrate, green tea extract, ascorbic acid, chromium nicotinate and cholecalciferol (HUM5007) will increase the resting metabolic rate (RMR) of overweight subjects maintained on a calorie-restricted diet. In this randomized, double-blind, placebo-controlled, crossover trial, overweight adults on a calorie-restricted diet were randomized to three 7-day treatment periods with 7-Keto, HUM5007 or placebo. Resting metabolic rate was measured by indirect calorimetry at the beginning and end of each treatment period with a 7-day washout between testing periods. Of 45 subjects enrolled, 40 completed the study (30 women, 10 men; mean age, 38.5 years; mean body mass index, 32.0 kg/m^2). During the placebo treatment, RMR decreased by 3.9% (75±111 kcal/day; mean±S.D.); however, RMR increased significantly by 1.4% (21±115 kcal/day) and 3.4% (59±118 kcal/day) during the 7-Keto and HUM5007 treatment periods, respectively (each compared to placebo, $P=.001$). No significant differences were found between the treatment periods with respect to compliance or adverse events. In this study, the administration of HUM5007 or 7-Keto reversed the decrease in RMR normally associated with dieting. HUM5007 and 7-Keto increased RMR above basal levels and may benefit obese individuals with impaired energy expenditure. HUM5007 and 7-Keto were generally well tolerated and no serious adverse events were reported.

Keywords: 3-acetyl-7-oxo-dehydroepiandrosterone; Resting metabolic rate; Obesity; Weight loss; Clinical trial

1. Introduction

In the United States, 64% of adults are currently considered to be overweight and 30% are classified as obese [1]. In addition to limiting mobility and daily activities, obesity is a risk factor for a host of chronic disorders including hypertension, hyperlipidemia, diabetes mellitus and osteoarthritis, and has been associated with premature death from all causes [1–6]. Consequently, obesity and physical inactivity are the second leading cause of premature death in this country and are currently responsible for 400,000 deaths annually [7].

Obesity is a disorder of energy balance, occurring when energy expenditure is no longer in equilibrium with daily energy intake to ensure body weight homeostasis. Consequently, efforts to treat obesity must create a negative energy balance, utilizing stored fat as an energy source. Although approximately 74% of Americans are attempting to lose or maintain body weight [2], the majority of these efforts will not be successful.

In most weight loss programs, major emphasis is placed on manipulating diet and appetite; however, interest in pharmacologically increasing energy expenditure is increasing as such agents represent a new tool for the treatment of obesity [8]. Specifically, growing evidence supports the hypothesis that individuals with a low-energy phenotype may be predisposed to weight gain and obesity, as a result of low-energy output caused by a low resting metabolic rate (RMR), lack of physical activity or both [8,9].

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* Corresponding author. Tel.: +1 952 400 0402; fax: +1 952 937 7667.
E-mail address: john@zenk.net (J.L. Zenk).

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A significant problem with weight reduction programs is a result of changes in body metabolism over time. The fat-free mass (FFM) represents the most metabolically active body tissue and is the major determinant of RMR [10,11]; however, weight loss may be associated with a reduction in metabolic rate due to a decrease of FFM, partially explaining the difficulty in achieving and maintaining a lower body weight in some individuals [10–12].

As RMR represents 60% of total energy expenditure, compared to 30% as nonresting energy expenditure and 10% as heat [12], small increases in RMR may result in considerable energy consumption over time. Thus, even minimal increases in daily energy expenditure of 2–3% may have clinical relevance in preventing the decline in RMR associated with weight loss and in decreasing the risk of regaining the weight lost after successful dieting [8].

Increasing energy expenditure may be accomplished by activating the central or sympathetic nervous systems, thyroid hormones or other thermogenically futile cellular mechanisms [8,13]. Several substances with demonstrated ability to increase RMR have been combined into a single oral formulation (HUM5007) that is currently undergoing evaluation as an adjunctive treatment in calorie-restricted weight loss programs. Specifically, HUM5007 contains six ingredients: 3-acetyl-7-oxo-dehydroepiandrosterone (7-Keto, Humanetics Corporation, Eden Prairie, MN, USA), green tea extract, chromium nicotinate, calcium citrate, cholecalciferol (vitamin D_3) and ascorbic acid (vitamin C).

7-Keto is a naturally occurring metabolite of the adrenal steroid, dehydroepiandrosterone (DHEA). Preclinical studies in rats have shown that 7-Keto is more potent than DHEA for inducing the thermogenic enzymes glycerol-3-phosphate dehydrogenase and malic enzyme [14] and 7-Keto increases the rate of mitochondrial substrate oxidation, liver catalase activity and fatty acetyl-CoA oxidase activity [15] without activating the androgen receptor [16] or converting to other androgens or estrogens in the body [17,18]. Two placebo-controlled studies demonstrated significantly greater weight loss in subjects using 7-Keto (100 mg twice daily) than in those using placebo over 8 weeks when both were used in conjunction with a calorie-restricted diet and exercise program [19,20].

Green tea extract activates thermogenesis and fat oxidation, possibly via mechanisms involving the sympathetic nervous system [21] or by reducing fatty acid production by inhibiting fatty acid synthase [22,23].

While the mechanism remains unclear, the addition of chromium (usually 200 μg/day) to the diet has increased lipid metabolism in several controlled studies, resulting in statistically significant decreases in total body fat and increases in lean body mass compared to placebo-treated individuals [24–31]. Although chromium is an essential nutrient, normal dietary intake of chromium is often suboptimal in humans and chromium was therefore included in the HUM5007 formulation. Ascorbic acid was also added as it appears to promote intestinal chromium absorption [32].

Calcium has been shown to regulate adiposity by increasing lipolysis, preserving thermogenesis and accelerating weight and fat loss during caloric restriction [33–35]. Clinical and epidemiological data also suggest that, in the setting of a reduced caloric intake, increased dietary calcium accelerates fat loss and may contribute to a reduced risk of obesity [36–41]. Cholecalciferol, the active form of vitamin D, was added to the HUM5007 formulation to ensure intestinal absorption of calcium [42–47].

The following study was performed to test the hypothesis that the combined effects of the compounds in HUM5007, administered as a single formulation, to overweight adult subjects maintained on a calorie-restricted diet will result in greater RMR and resultant weight loss than the administration of 7-Keto alone.

2. Methods and materials

2.1. Subjects

Healthy subjects aged 20 to 50 years with a BMI ≥ 25 but ≤ 40 kg/m^2 were enrolled in the study. Exclusion criteria included any evidence of an eating disorder, such as anorexia or bulimia, or the presence of any illness that might represent a potential cause of weight loss. Subjects were also excluded if they were using medications for weight loss or were pregnant or lactating.

2.2. Protocol

This 5-week study utilized a randomized, double-blind, placebo-controlled, three-way crossover design. A 7-day screening period was followed by each of the three 7-day study periods separated by a 7-day washout period. At the initial screening visit, a medical history and physical exam were completed and vital signs, bioelectric impedance analysis (BIA) and fasting RMR were measured. Qualified subjects returned to the clinic for their baseline visit where they were counseled by the study dietitian regarding their calorie-restricted diet. Baseline outcome and safety measures were performed, and patients were randomized to receive one of the three study medications in double-blind fashion, then discharged with instructions to take two capsules of test article twice daily (morning and evening) and to follow their prescribed diet for 7 days. On Day 8, subjects returned to the clinic for measurement of vital signs, BIA and RMR, and assessment of adverse events. The subjects then entered a 7-day washout period without caloric restriction before returning for baseline outcome and safety measures and receiving another 7-day supply of double-blind test article or placebo. This procedure was repeated in an identical manner for each of the three treatment periods. An independent statistician prepared the randomization table and the investigators were blinded to the code assignments and the randomization procedure.

2.3. Study diet calculations and subject instructions

Subjects were prescribed calorie-restricted diets based on their baseline RMR. The RMR was determined following a 12-h fast, and the total daily energy expenditure was estimated by multiplying RMR by 1.2. Daily caloric intake was established at 800 kcal less than the estimated daily energy requirement. The caloric composition of the diet was 45% carbohydrate, 25% protein and 30% fat. Subjects were asked to complete a daily food diary on two designated days each week. During the screening and washout periods, subjects were instructed to disregard their calorie-restricted diet and to resume their normal diet until the next treatment. Subjects were instructed to maintain their current activity and exercise routine throughout the study and to abstain from caffeinated beverages and tobacco products. Compliance was assessed by the review of a daily food diary on two designated days during each study week and by pill count.

2.4. Measurements

All measurements were obtained at baseline and at the beginning and end of each treatment period. The primary outcome variable was RMR, measured by indirect calorimetry using an open-circuit ventilated-hood system (Deltatrac II Metabolic Monitor, Sensor Medics Corp, Yorba Linda, CA, USA). Except for water, subjects fasted for 12 h prior to the RMR measurements. Subjects rested for 15 min prior to RMR measurement and were then placed alone in a recumbent position in a quiet, dimly lit, temperature-controlled room where they underwent 25 min of respiratory sampling under the hood. The metabolic monitor recorded energy expenditure readings in 1-min intervals. The final 20 min of readings was averaged to arrive at the RMR for that visit. Secondary outcome measures included changes in body mass index (BMI) and total body water (TBW) (Quantum II Bioelectric Impedance Analysis Instrument with Cyprus 1.2 software; RJL Systems, Clinton Township, MI, USA).

2.5. Test article composition

Each capsule of HUM5007 contained 250 mg calcium citrate, 150 mg green tea extract (standardized for 50% epigallocatechin gallate), 50 mg 3-acetyl-7-oxo-dehydroepiandrosterone, 50 mg ascorbic acid, 0.1 mg chromium nicotinate and 0.0025 mg cholecalciferol. Each capsule of 7-Keto contained 50 mg 3-acetyl-7-oxo-dehydroepiandrosterone and 450 mg rice powder. Placebo capsules contained 500 mg rice powder (Humanetics Corporation).

2.6. Statistical analyses

Baseline characteristics of each group were compared using matched pair *t*-tests. The computed change from baseline was compared for all measured variables and expressed as the mean, with variability expressed as the standard deviation (SD) of the change from baseline. Matched pair *t*-tests were used to compare the change in scores for each measured variable except for capsule discrepancy and adverse events where nonparametric Wilcoxon tests were used. Subjects who did not complete the study were excluded from analysis. Statistical significance was established at $P < .05$.

2.7. Ethics

The protocol and all advertisements for study participation were approved by a commercial IRB. All subjects provided written informed consent prior to participation in any trial activities.

3. Results

3.1. Study population

Forty-five subjects (34 women, 11 men) were enrolled in the study. Mean age was 38.6 years (range, 23–47 years), mean body weight was 93.7 kg (range, 71.6–124.4 kg) and mean BMI was 32.2 kg/m^2 (range, 26.1–40.3 kg/m^2). Of the 45 subjects randomized, 40 completed the study (30 women, 10 men) and 5 withdrew from the study: one suffered an ankle fracture unrelated to the study protocol or test article; one relocated from the area; and three withdrew due to personal scheduling conflicts. No significant differences were found between baseline characteristics of each study group prior to each treatment period (Table 1).

3.2. Resting metabolic rate

The mean change in RMR (SD; %) from baseline for each of the treatment periods is provided in Table 2. Subjects displayed a decrease of −75 kcal/day (111; −3.93%) during treatment with placebo; however, RMR increased by 59 kcal/day (118; 3.36%) and 21 kcal/day (115; 1.43%) during treatment with HUM5007 and 7-Keto, respectively. While these changes with HUM5007 and 7-Keto were significantly different than the placebo treatment phase (for each, $P=.001$), they were not significantly different from each other ($P=.110$; Table 2).

3.3. Between-treatment analysis of secondary outcome variables

No significant differences were noted in any of the secondary outcome variables when compared to placebo;

Table 1
Baseline characteristics

Variable ($N=40$)	HUM5007	7-Keto	Placebo
Mean resting metabolic rate, kcal/day	1763 (283)	1771 (298)	1777 (239)
Mean BMI, kg/m^2	32.1 (4.1)	31.9 (4.2)	32.0 (4.2)
Mean body weight, kg	93.2 (14.5)	92.9 (14.8)	93.1 (14.5)
Percent body fat	39.6% (9.8)	39.8% (9.7)	39.7% (9.8)
Percent TBW, %	47.0% (5.5)	47.0% (5.4)	46.8% (5.5)
Mean total caloric intake, kcal/day	1723.2 (702.3)	1642.3 (651.5)	1682.6 (643.6)

Values in parentheses are standard deviation.

Table 2
Treatment outcomes

	HUM5007	7-Keto	Placebo	HUM5007 vs. placebo	7-Keto vs. placebo	HUM5007 vs. 7-Keto
Primary outcome measures						
Pre-RMR, kcal/day	1763	1771	1777	–	–	–
Post-RMR, kcal/day	1821	1792	1702	–	–	–
Mean change from baseline (SD)	59 (118)	21 (115)	−75 (111)	–	–	–
Percent change from baseline (SD)	3.36% (6.67)	1.43% (5.95)	−3.93% (5.77)	–	–	–
Mean difference, kcal/day	–	–	–	134 (168)	96 (161)	37 (142)
Percent difference (SD)	–	–	–	7.29% (9.18)	5.36% (8.72)	1.93% (7.90)
P value (matched pair *t*-test)	–	–	–	0.001	0.001	NS
Secondary outcome measures						
BMI, kg/m^2	−0.22 (0.42)	−0.11 (0.42)	−0.19 (0.35)	NS	NS	NS
Body weight, kg	−0.56 (0.96)	−0.38 (1.15)	−0.55 (0.99)	NS	NS	NS
Body fat, %	0.15 (1.20)	−0.50 (1.38)	0.04 (1.18)	NS	NS	NS
Total body water, %	−0.25 (1.06)	0.37 (1.24)	−0.08 (1.00)	NS	NS	**0.04**
Total calorie intake, kcal/day	−444.5 (600.6)	−263.9 (624.8)	−281.8 (578.1)	NS	NS	NS
Dietary carbohydrate, g	−61.0 (83.8)	−27.2 (75.5)	−45.6 (84.2)	NS	NS	NS
Dietary protein, g	−2.7 (28.8)	−6.4 (35.5)	0.4 (30.7)	NS	NS	NS
Dietary fat, g	−21.1 (30.7)	−14.4 (35.7)	−11.2 (29.6)	NS	NS	NS

however, a change from baseline in TBW percent (TBW%) was found when comparing HUM5007 to 7-Keto. Although this difference was identified as statistically significant, it may not be clinically relevant as it amounted to less than a 1% difference between 7-Keto and HUM5007 for the change in TBW (Table 2).

3.4. Safety and tolerability

No serious adverse events were encountered during any of the treatment periods. Table 3 lists the incidence of all adverse events. No significant between-group differences were found in vital signs, treatment compliance, or the number or type of adverse events experienced by the subjects. Of six adverse events recorded during treatment with HUM5007, three were considered to be related to the test article: flatulence, nausea and palpitations. Of eight adverse events recorded during treatment with 7-Keto, three were considered to be related to the test article: nausea (2) and vertigo. Five adverse events occurred during the placebo treatment period [diarrhea, flatulence, palpitations, upper respiratory infection (2)].

4. Discussion

As expected, the individuals enrolled in the current study demonstrated a substantial decline in RMR (−3.9%) when subjected to a calorie-restricted diet; however, the twice-daily administration of either HUM5007 or 7-Keto for 7 days resulted in substantial increases in RMR of 3.4% and 1.4%, respectively, above baseline levels. When compared to RMR during periods of calorie-restriction alone, these increases become clinically significant. Compared to the placebo treatment period, the increase in RMR following HUM5007 treatment was 134 kcal/day (7.3%) and 96 kcal/day (5.4%) after similar treatment with 7-Keto. No significant differences between treatment groups with respect to the quantities of carbohydrate, protein, fat or total calories consumed at baseline or during any of the treatment periods were found. Therefore, the significant increases in RMR associated with the administration of HUM5007 and 7-Keto in this study appear to be due to pharmacologically induced increases in resting energy expenditure in these individuals.

Although the change in RMR produced by HUM5007 was numerically superior to that of 7-Keto, this difference was not statistically significant. We propose that a 7-day treatment period may not have been sufficient for the maximal difference between these agents to become apparent and that a study of longer duration should be performed to further compare the effects of HUM5007 and 7-Keto on RMR in obese subjects.

The finding that some obese individuals have an impaired capacity for energy expenditure which may have been acquired through genetic, environmental and/or dietary factors is now well established [48–52]. This may explain their proclivity to become obese and to regain weight following initially successful weight loss efforts, despite the maintenance of persistent, low-energy intake [53–55]. In addition, the decline in RMR that occurs during caloric restriction [56], as demonstrated in the present study, may further increase the incidence of diet

Table 3
Incidence of adverse events

	HUM5007	7-Keto	Placebo
Diarrhea	–	–	1
Flatulence	1	–	1
Knee injury	1	–	–
Nausea	1	2	–
Palpitations	1	–	1
Shoulder injury	–	1	–
Upper respiratory infection	2	4	2
Vertigo	–	1	–

failure. In support of this concept, a recent meta-analysis of published studies ($n=12$) described the metabolic characteristics of formerly obese individuals compared to weight-matched controls and revealed that the mean RMR was 3–5% lower in the formerly obese subjects than among control subjects who were never obese [57]. Consequently, agents that demonstrate an ability to increase daily energy expenditure (RMR) are receiving much research attention and potential new compounds with a variety of thermogenic mechanisms are being investigated. A review of available compounds noted that, due to a myriad of problems in the development of these agents, expectations of large increases in RMR should be lowered and that new compounds with the ability to increase daily RMR by as little as 2% should be considered as strong candidates for clinical development [6].

In the present study, treatment with HUM5007 and 7-Keto was generally well tolerated. Adverse events were relatively few, self-limiting and none resulted in discontinuation from the trial. Obese participants demonstrated a 5.4% and 7.3% increase in daily RMR with 7-Keto and HUM5007, respectively (compared to placebo), while maintaining a calorie-restricted diet. This clinically relevant magnitude of RMR increase induced by 7-Keto and HUM5007 indicates that these are two possible treatment options for enhancing thermogenesis and therefore weight loss in obese individuals maintained on calorie-restricted diets. A statistically significant difference was noted in (mean; SD) TBW% (a secondary outcome variable) between 7-Keto (0.37%; 1.24) and HUM5007 treatments (−0.25%; 1.06) ($P=.04$); however, these changes appear to be too small to be of clinical significance.

The results of this study reveal that administration of HUM5007 or 7-Keto to overweight adults in conjunction with a calorie-restricted diet safely reverses the decline in RMR normally associated with dieting. HUM5007 and 7-Keto also demonstrated an ability to increase RMR above basal levels and may be a benefit to obese individuals with impaired energy expenditure.

Future research should include comparative studies of longer duration to further assess the potential benefit of these two agents for promoting long-term weight maintenance in obese subjects, particularly those with a low-energy phenotype.

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