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Placebo-controlled pilot study of ramelteon for adiposity and lipids in patients with schizophrenia

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Abstract

Objective—Few interventions have been successful to prevent or reverse the medical complications associated with antipsychotic agents in the schizophrenia population. In particular, no single agent can correct multiple metabolic abnormalities such as insulin resistance, hyperlipidemia, inflammation, obesity and fat distribution. We now report a randomized placebo-controlled pilot study to examine the effects of ramelteon on obesity and metabolic disturbances among subjects with schizophrenia.

Methods—A double-blind, placebo-controlled, 8-week pilot trial was conducted, adding ramelteon 8 mg/day to stable outpatients with schizophrenia. Vital signs, anthropometric measurements, including height, weight, waist circumference, and body fat were assessed and laboratory assays were tracked to monitor changes in metabolic markers.

Results—Twenty-five subjects were randomly assigned to treatment with study drug or placebo and twenty subjects were included in the final analysis. Ramelteon did not improve anthropometric measurements, glucose metabolism and inflammatory markers. There was, however, a significant decrease in total cholesterol and cholesterol to HDL ratio in the ramelteon group. While the standard anthropometric measures did not show significant change, the DEXA scan showed a trend toward reduction in fat in the abdominal and trunk areas with a moderate effect size.

Conclusions—While ramelteon decreased cholesterol, treatment may have to be longer than 8 weeks and with a higher dose for maximal effect of ramelteon for body fat and lipid changes. Future studies are needed for patients with schizophrenia with a larger sample size to fully understand ramelteon's effects on abdominal adiposity and lipids.

Keywords

ramelteon; schizophrenia; obesity; insulin resistance; glucose metabolism

The prevalence of obesity among individuals with schizophrenia and schizoaffective disorders is 1.5 – 2.0 times higher than in the general population (1). This increased obesity rate is, in part, related to factors such as poor diet and sedentary lifestyle. The use of atypical

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antipsychotics, however, may contribute to obesity as they have been linked to weight gain and obesity, along with increased risk of other metabolic complications including dyslipidemia, diabetes, and the possible associated risk of cardiovascular diseases (2–3). In a study with non-obese schizophrenia patients, both clozapine- and olanzapine-treated groups showed significant insulin resistance and impairment of glucose effectiveness, as measured by a frequently sampled intravenous glucose tolerance test compared with a risperidone-treated group (4).

Individuals with insulin resistance commonly have an abnormal fat distribution that is characterized by greater abdominal body fat, which can accumulate intraperitoneally (visceral fat). Studies have found that excess visceral fat is more strongly associated with insulin resistance than any other adipose tissue compartment(5–6). Regardless of the relative contributions of visceral fat and abdominal subcutaneous fat to insulin resistance, a pattern of abdominal (or upper body) obesity correlates more strongly with insulin resistance and the metabolic syndrome than does lower body obesity (7).

Melatonin and Ramelteon

Nocturnal plasma melatonin concentrations are decreased in drug-free patients with schizophrenia and there is no correction in the pattern even after patients improve with antipsychotic agents (8). A recent 8-week study found that olanzapine treatment in rats induced significant increases in weight and visceral adiposity, as well as a significant 55% reduction in nocturnal plasma melatonin. Melatonin was administered to restore to control levels (9). Body weight increased 18% in rats treated with olanzapine alone, 10% with olanzapine plus melatonin, 5% with melatonin alone and 7% with control vehicle (9).

To date, few interventions have been successful to prevent or reverse the medical complications associated with antipsychotic agents in the schizophrenia population. In particular, no single agent has been able to address critical metabolic abnormalities such as insulin resistance, hyperlipidemia, inflammation, obesity and fat distribution. A number of studies used melatonin for sleep disturbances in schizophrenia (10–12). However, none of these studies have examined the effect of melatonin on the antipsychotic drug-induced weight gain, in humans.

Ramelteon is a novel MT1 and MT2 melatonin receptor selective agonist which was recently approved by the Food and Drug Administration (FDA) for insomnia treatment. Ramelteon has minimal affinity for other receptors implicated in potential abuse and impairment, such as the benzodiazepine receptors, dopamine receptors, opiate receptors, and ion channels (13). Ramelteon, in addition to being a treatment for insomnia and sleep cycle disturbances, might be able to improve metabolic abnormalities in the schizophrenia population. The goal of this pilot study was to examine the effects of ramelteon 8mg/day on adiposity and lipids among schizophrenia subjects treated with antipsychotic agents. The primary specific aims of the study was to examine the efficacy of ramelteon, compared to placebo, in reducing waist circumference (cm) and abdominal fat as measured by dual-energy X-ray absorptiometry (DEXA) and to examine the efficacy of ramelteon in improving insulin resistance as measured by the homeostatic model assessment of insulin resistance (HOMA-IR).

METHODS

Subjects were recruited from the Freedom Trial Clinic at the Erich Lindemann Mental Health Center and were studied at the Mallinckrodt General Clinical Research Center (GCRC) at the Massachusetts General Hospital (MGH), Boston. The study was approved by the institutional review boards of MGH and the Massachusetts Department of Mental Health

(DMH). Data was collected from March 2008 to October 2009. Thirty-one male and female outpatients between the ages of 18 and 65 years with the diagnosis of schizophrenia or schizoaffective disorder were screened for the study. After providing written informed consent, subjects underwent a diagnostic evaluation by a research psychiatrist using the Structured Clinical Interview for DSM-IV (SCID) (14). Subjects who were treated with clozapine, olanzapine, risperidone or quetiapine were eligible for participation. Additionally, subjects were required to have a BMI of $> 27 \text{ Kg/m}^2$ with evidence of insulin resistance or any component of metabolic syndrome (fasting insulin $> 15 \text{ mU/liter}$, HOMA-IR > 2 , fasting glucose 100 mg/dL , fasting triglycerides 150 mg/dL , abdominal girth 102 cm [40 inches] in men or 88 cm [35inches] in women, HDL-Cholesterol 40 mg/dL in men or 50 mg/dL in women, or blood pressure $130/85 \text{ mm Hg}$) or a BMI of 30 Kg/m^2 .

Subjects were excluded on the basis of inability to provide informed consent, current substance abuse; Type 1 or 2 DM or fasting glucose 126 mg/dL ; untreated thyroid disease; pregnancy; significant medical illness including severe cardiovascular, hepatic, or renal diseases (serum creatinine > 1.5); or unstable psychiatric illness (CGI's severity of illness question of 5 or greater or a baseline Total PANSS score > 80). Subjects treated with the following medication known to affect glucose tolerance were also excluded: birth control pills containing norgestrel, steroids, beta-blockers, anti-inflammatory drugs (including aspirin and ibuprofen), thiazide diuretics and agents that induce weight loss. Similarly, subjects treated with fluvoxamine, ketoconazole, or fluconazole (strong CYP2C9 inhibitor) or a known hypersensitivity to ramelteon or to any of its components, were excluded from the study. Study subjects received a 2-week supply of ramelteon or placebo (14 tablets) plus an additional 3 tablets for assessing compliance. Study subjects were also counseled and instructed to avoid high-fat meals with or immediately before taking ramelteon/placebo, since there has been some evidence that the absorption of ramelteon has been delayed following consumption of a high-fat meal (15). Subjects were instructed to take ramelteon/placebo within 30 minutes before going to bed and activities were confined to preparing for bed.

Anthropometric Measures

Anthropometric measurements, such as height, weight, circumferences, skin fold and body fat were conducted utilizing previously reported methods (16–17). Body composition was measured by using whole-body dual-energy X-ray absorptiometry (DEXA) (Hologic QDR-4500; Hologic Inc, Waltham, MA). DEXA has been validated for body-composition measurements (18–19) with correlations of 0.99 with a 4-compartment-model body-composition method for measuring total mass (fat and lean), fat-free mass and 0.93–0.97 with multi-slice computed tomography for measuring regional fat-free mass (18–19). Percentage trunk fat, percentage trunk lean body mass (LBM) was calculated from whole-body DEXA.

Laboratory Assays

Laboratory assays were performed by the chemistry laboratory and the MGH GCRC Core Laboratory. Insulin immunometric assays were performed using an Immulite Analyzer (Diagnostic Product Corp; Los Angeles, CA) with an intra-assay coefficient of variation of 4.2% to 7.6%. The standard fasting lipids were measured utilizing conventional blood analysis. Low-density lipoprotein cholesterol (LDL-C) values were estimated indirectly for participants with plasma triglyceride levels less than 400 mg/dL (4.52 mmol/L) and directly if the triglyceride was $> 400 \text{ mg/dL}$ (20). Lipoprotein particle measurements were done by nuclear magnetic resonance spectroscopy (Liposcience, Inc., Raleigh, NC) and yielded LDL particle size and number, large HDL (high density lipoprotein) particle size, VLDL (very low density lipoprotein) particle size and small LDL particle number. CRP was measured

via a high-sensitivity latex-enhanced immunonephelometric assay on a BN II analyzer (Dade Behring, Newark, Del). The HOMA-IR was calculated by the following formula: fasting serum insulin concentration $\times$ fasting plasma glucose concentration/22.5 (21–22).

Psychopathology, Sleep, and Assessment for Treatment Emergent Events

Positive and Negative Symptom Subscale (PANSS) (23), the Hamilton rating Scale for Depression (HAM-D) (24) and the Heinrichs Carpenter Quality of Life Scale (QOL) (25) were used to assess psychopathology. The Stanford Sleepiness Scale (SSS), the Fatigue Scale Inventory (FSI) (26), and the Medical Outcomes Study Sleep Scale (MOS-SS) (27) were used to assess ramelteon's effect on sleep. The Systematic Assessment for Treatment Emergent Events (SAFTEE) (28) consisting of General inquiry and the Systematic inquiry to assess possible side effects was performed at baseline and repeated at week 4 and 8.

Statistical Analysis

Statistical analysis was performed using SPSS (version 15.0, Chicago, IL). For all analyses, a p value less than 0.05 (2-tailed) was used for statistical significance. Descriptive statistics were used to describe demographic and clinical characteristics of the study sample. Chi-square was used to access differences in frequency. Group comparisons were performed using independent t test for continuous variables and Chi-square test for categorical variables. Analysis of covariance (ANCOVA) was used to examine change scores from baseline to week 8 between groups after controlling for baseline scores. Effect size for selected variables was calculated using Cohen's D.

RESULTS

Demographics

Thirty-one subjects consented for the study with 25 subjects randomized to either ramelteon 8 mg/day or placebo in a 2:1 fashion. Five subjects withdrew consent following randomization but prior to the week 4 assessment (2 ramelteon and 3 placebo). Data from 20 subjects is presented. Baseline demographics are presented in Table 1. There were no differences between the placebo and ramelteon groups for mean age, gender, ethnicity or antipsychotic drug use. Four subjects in the ramelteon group were treated with two antipsychotic agents compared to one subject in the placebo group (Table 1).

Anthropometric measurements and DEXA

Anthropometric measurements at baseline did not differ in the placebo group compared to the ramelteon group. There was no significant difference between groups comparing week 8 values, controlling for baseline for body weight, BMI, waist circumference, waist-hip ratio, and skin fold total, and ideal body weight (Table 2). Though not statistically significant, there was a decrease in the ramelteon group compared to the placebo group in mean change in abdominal fat ($p=.07$, effect size=.88), trunk fat ($p=.45$, effect size=.40), percent abdominal fat ($p=.18$, effect size=.72) and percent trunk fat ($p=.29$, effect size=.56) at week 8 controlling for baseline (Table 3). While there was a non-significant increase in lean abdominal mass and trunk mass in the ramelteon group, there was a decrease in these measures in the placebo group. Overall the abdominal ($p=.44$) and trunk mass (fat and lean) ($p=.44$) non-significantly decreased in the ramelteon group while it increased in the placebo group.

Glucose metabolism and inflammatory marker

The ramelteon group had non-significant reductions in fasting serum insulin level ($p=.29$, effect size= 0.6) and HOMA-IR ($p=.34$, effect size=.54) compared to placebo (Table 2).

The ramelteon group had a greater decrease in C-reactive protein but this was not significant ($p=.55$).

Lipids

The ramelteon group showed a significant decrease in total cholesterol and cholesterol to HDL ratio ($p=.03$ and $.01$, respectively) (Table 2). LDL-cholesterol decreased in the ramelteon group but was not significant ($p=.10$, effect size = $.76$). There was a significant reduction in LDL particle number in the ramelteon group (1785 ± 513 nmol/L to 1626 ± 606 nmol/L; effect size = 0.53 ; $p=0.03$). There was a non-significant reduction in small LDL in the ramelteon group and trend toward an increase in LDL-C particle size in the ramelteon group (20.77 ± 0.99 nm to 20.81 ± 0.8 nm; effect size = $.49$; $p= .36$). The decrease in small LDL particle number and the increase in LDL-C particle size suggest improvements in atherogenic LDL-cholesterol in the ramelteon group.

Psychopathology, sleep quality, and side effects

There were no significant changes in psychopathology in either group from the baseline to week 8. Examining changes in sleep, the ramelteon group experienced a trend toward less daytime fatigue ($p=.05$, effect size = 1.08) and fewer days that they felt fatigued ($p=.09$, effect size = 1.27) compared to placebo. Frequently observed side-effects, compared to placebo, during the study were drowsiness (57% vs. 33%), heart burn (21% vs. 0%), cough (21% vs. 0%), akathisia (21% vs. 0%), increased urinary frequency (14% vs. 0%), and problems with memory or concentration (21% vs. 0%). The placebo group experienced arthralgia/myalgia and anxiety at significantly higher rates than the ramelteon group.

DISCUSSION

The primary aims of this pilot study were to examine the effects of ramelteon 8mg/day on lipids and on measurements of adiposity including weight, waist measurements, and body composition based on DEXA scan. Studies in melatonin research have suggested that ramelteon might be able to improve metabolic abnormalities seen in patients with schizophrenia (9, 29). None of the previous studies have examined the effect of melatonin on the antipsychotic drug-induced weight gain in humans. We found beneficial changes in lipids such as a significant decrease in total cholesterol and cholesterol to HDL ratio as well as a trend toward favorable reductions in small LDL particle number and increases in LDL-c particle size. CRP also decreased, although not significantly, suggesting potential reduction in inflammation. While the standard anthropometric measures in the current study did not show significant changes, data from the DEXA scan suggests that there was a trend toward reduction in fat in the abdominal and trunk areas with a moderate effect size.

Ramelteon was well tolerated and no patients discontinued the treatment because of side effects. Ramelteon did not appear to have a great affect on sleep or overall activity. One possible reason for this is that subjects were already taking sedating antipsychotic agents. Additionally, the overall benefit of ramelteon may have been reduced as the majority of subjects smoked cigarettes. CYP1A2 is the major isozyme involved in the hepatic metabolism of ramelteon; the CYP2C subfamily and CYP3A4 isozymes are also involved to a minor degree (30). Cigarette smoke is known to induce CYP1A2 (31). As 93% of subjects receiving ramelteon were smokers, it is possible that the dose was inadequate to show maximal benefits. Future studies with higher doses for the patients with schizophrenia who smoke are warranted.

Our findings in this study were limited by the small sample size. It is possible that with a larger sample, significant improvements might be observed not only in adiposity and lipid

metabolism, but also in inflammatory markers such as CRP and measures of glucose metabolism. It is also possible that higher dose of ramelteon would be more clinically useful in this population, along with a greater length of time for observation. Additionally, ramelteon should be examined as a preventive measure for patients with schizophrenia taking antipsychotic medication. It is possible that ramelteon could be effective before metabolic abnormalities are induced among these patients.

In conclusion, although the sample size was small, the statistical improvements in total cholesterol and cholesterol to HDL ratio in the ramelteon group may potentially ameliorate some metabolic side effects of antipsychotic medications in patients with schizophrenia. Further clinical trials with ramelteon in subjects with schizophrenia to evaluate reduction in obesity and metabolic disturbances among patients with schizophrenia are warranted.

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Demographic and clinical characteristics, comparing ramelteon 8 mg/day to placebo in an 8-week pilot study in subjects with schizophrenia

Table 1

	Placebo (N=6)			Ramelteon (N=14)			t	df	p
	Mean	SD	N	Mean	SD	N			
Age, years	56	9	49	7	1.67	1	0.14		
	N	%	N	%	x ²	df	p		
Sex					1.27	1	0.26		
Male	5	83	8	57					
Female	1	17	6	43					
Race					0.42	1	0.52		
Caucasian	5	83	13	93					
Hispanic	1	17	1	7					
African-American	0	0	0	0					
Other	0	0	0	0					
Diagnosis					0.47	1	0.49		
Schizoaffective Disorder	2	33	7	50					
Schizophrenia	4	67	7	50					
Education Level					8.66	1	0.69		
Middle School	3	50	9	64					
Some High School	1	17	3	21					
H.S. Diploma/GED	2	33	1	7					
Some College	0	0	1	7					
College Graduate	0	0	0	0					
Primary Antipsychotic					4.67	3	0.2		
Clozapine	3	50	8	57.1					
Olanzapine	0	0	4	28.6					
Quetiapine	2	33.3	0	0					
Risperidone	1	16.7	2	14.3					
Alcohol use					2.3	1	0.69		

	Placebo (N=6)			Ramelteon (N=14)			t	df	p
	Mean	SD		Mean	SD				
Yes	2	33		1	93				
No	4	67		13	7				
Tobacco use							0.16	1	0.69
Yes	4	67		13	93				
No	2	33		1	7				
Caffeine Use							0.49	1	0.49
Yes	6	100		13	93				
No	0	0		1	7				

Outcome measures comparing ramelteon 8mg/day to placebo in an 8-week pilot study in subjects with schizophrenia

Table 2

	Placebo (N = 6)						Ramelteon (N = 14)					
	Baseline			Week 8			Baseline			Week 8		
	Mean	SD		Mean	SD		Mean	SD		Mean	SD	ANCOVA
Anthropometric measurements												
Body weight, kg	92.57	7.43		91.73	8.18		82.51	8.55		82.66	9.15	1, 18 0.28
Body mass index, kg/m ²	33.27	6.03		32.95	5.89		29.87	3.32		29.93	3.62	1, 18 0.23
Waist circumference, cm	109.45	6.59		108.37	6.5		106.91	9.56		106.09	8.8	1, 18 0.87
Waist-hip ratio	0.98	0.06		0.99	0.08		1	0.06		1.01	0.06	1, 18 0.66
Body fat, %	32.53	6.43		33.73	6.41		31.84*	6.92*		32.62	6.79	1, 17 0.79
Glucose metabolism measurements												
Fasting plasma glucose, mg/dL	92.33	12.23		90.83	18.92		84.5	19.81		85.71	18.46	1, 18 0.78
Fasting serum insulin, µIU/mL	8.1**	5.27**		9.88	5.59		13.5	9.56		11	4.72	1, 17 0.29
HOMA-IR	1.97**	1.6**		2.36	1.73		2.93	2.27		2.4	1.51	1, 17 0.34
HbA1c, %	5.45	0.38		5.45	0.56		5.74	0.6		5.82	0.81	1, 18 0.61
CRP, mg/L	5.1	9.04		4.52	6.45		7.39	8.44		5.02*	4.8*	1, 17 0.55
Conventional lipid panel												
LDL-C, mg/dL	102.33	29.53		104.83	31.8		126.5	29.44		117.07	31.10	1, 18 0.10
HDL-C, mg/dL	43.5	7.29		38.83	3.54		41.79	7.39		40.71	6.79	1, 18 0.56
Triglycerides, mg/dL	128.5	46.5		157.83	79.35		183.14	113.18		186.43	100.22	1, 18 0.12
Total Cholesterol, mg/dL	171.33	36.71		175.17	35.81		205	39.38		195.21	42.07	1, 18 0.03
Cholesterol HDL Ratio	4.01	1.01		4.56	1.42		5.07	1.42		4.85	1.33	1, 17 0.01
NMR lipoprotein particle measures												
LDL Particle Number, nmol/L	1320.67	308.15		1291.5	381.91		1785.14	512.97		1625.86	606.21	1, 18 0.03
LDL Particle Size, nm	20.53	0.52		20.57	0.43		20.77	0.99		20.81	0.93	1, 18 0.36

	Placebo (N = 6)				Ramelteon (N = 14)						
	Baseline		Week 8		Baseline		Week 8		ANCOVA		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p
Large HDL Particle Size, nm	7.75	3.9	5.65	2.43	5.97	4.18	6.11	4.04	0.26	1, 18	0.62
Large VLDL Particle Size, nm	2.67	2.61	5.13	6.42	7.26	8.09	6.57	6.29	1.79	1, 18	0.20
Small LDL Particle Number, nmol/L	904.67	251.25	888	349.73	1215.36	649.73	1066.93	647.31	3.10	1, 18	0.10

HOMA-IR: Homeostasis model assessment of insulin resistance; HbA1c: Glycosylated hemoglobin; CRP: C-reactive protein; BUN: Blood Urea Nitrogen; ALT (SGPT): Alanine Aminotransferase (Serum Glutamate Pyruvate Transaminase)

* N = 13;
** N=5

Table 3

DEXA scan results, comparing ramelteon 8mg/day to placebo in an 8-week pilot study in subjects with schizophrenia

	Placebo (N = 6)						Ramelteon (N = 14)					
	Baseline		Week 8		Baseline		Week 8		Baseline		Week 8	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Area, cm												
Abdominal	74.28	12.57	77.58	15.29	62.94	15.44	62.72	10.45	1.18	1.18	1.18	0.29
Total	2201.25	252.62	2226.07	242.23	2089.39	175.85	2099.07	164.30	0.59	1.18	0.45	0.45
BMD, g/cm ²												
Abdominal	1.35	0.55	1.39	0.58	1.04	0.18	1.04	0.18	0.96	1.18	0.34	0.34
Total	1.15	0.12	1.16	0.11	1.12	0.06	1.11	0.06	2.30	1.18	0.15	0.15
BMC, g												
Trunk	699.26	89.28	721.52	96.95	622.59	94.51	608.99	76.16	3.91	1.18	0.06	0.06
Abdominal	102.23	51.54	111.62	64.62	66.03	24.50	65.39	17.59	3.25	1.18	0.09	0.09
Total	2550.47	513.93	2594.00	490.27	2334.09	283.01	2329.46	268.38	5.04	1.18	0.04	0.04
Fat, g												
Trunk	15858.17	3849.21	15793.42	3973.07	14719.13	4631.40	14374.91	4431.66	0.61	1.18	0.45	0.45
Abdominal	4988.52	1470.79	5120.92	1770.58	4151.79	1319.32	3934.86	1151.97	3.66	1.18	0.07	0.07
Total	31699.70	9698.86	31621.28	9894.11	26870.46	8087.34	26651.49	8068.40	0.09	1.18	0.77	0.77
Fat %												
Trunk	33.95	7.65	34.15	7.53	33.53	7.84	32.86	7.69	1.18	1.18	0.29	0.29
Abdominal	35.77	7.42	36.03	7.71	34.32	7.04	33.04	6.56	1.95	1.18	0.18	0.18
Total	33.33	8.49	33.60	8.83	31.64	7.57	31.29	7.54	0.67	1.18	0.43	0.43
Lean, g												
Trunk	30064.30	3699.33	29557.22	3878.67	27923.74	2919.62	28215.06	3220.93	1.95	1.18	0.18	0.18
Abdominal	8741.52	1232.37	8689.13	777.87	7770.13	1365.21	7827.89	1216.74	0.20	1.18	0.66	0.66
Total	60088.08	6806.02	59084.92	7409.14	54746.27	5531.48	55273.89	6067.22	2.96	1.18	0.10	0.10
Lean & BMC, g												
Trunk	30763.53	3773.82	30278.70	3937.43	28546.32	2953.33	28824.06	3255.71	1.80	1.18	0.20	0.20
Abdominal	8843.77	1257.40	8800.75	806.65	7836.16	1375.39	7889.06	1221.16	0.15	1.18	0.70	0.70
Total	62638.57	7190.11	61678.88	7840.35	57080.36	5703.03	57603.34	6227.94	2.84	1.18	0.11	0.11

		Placebo (N = 6)				Ramelteon (N = 14)				ANCOVA		
		Baseline		Week 8		Baseline		Week 8				
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p
Total Mass, g												
Trunk		46621.70	3074.96	46072.13	4441.93	43265.45	4961.18	43198.98	5042.99	0.64	1, 18	0.44
Abdominal		13832.27	1881.11	13921.67	2034.18	11987.96	2125.05	11823.92	1806.17	0.63	1, 18	0.44
Total		94338.27	7395.40	93300.17	8168.12	83950.82	8143.20	84254.84	8699.22	2.44	1, 18	0.14

BMD: Bone Mineral Density; BMC: Bone Mineral Content