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► **To cite this version:**

Elizabeth Louise Thomas, Aidan Makwana, Rexford Newbould, Anil Rao, Giulio Gambarota, et al..
Pragmatic study of orlistat 60mg on abdominal obesity. *European Journal of Clinical Nutrition*, 2011,
10.1038/ejcn.2011.108 . hal-00654480

HAL Id: hal-00654480

<https://hal.science/hal-00654480>

Submitted on 22 Dec 2011

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Pragmatic study of orlistat 60mg on abdominal obesity

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Word counts for abstract: 219 and text: 2,998

Running Title: orlistat 60mg and abdominal obesity

Abstract

Background and Aims: It is well established combining a reduced calorie, low fat diet with the lipase inhibitor orlistat, results in significantly greater weight loss than placebo plus diet. This weight loss is accompanied by changes in adipose tissue (AT) distribution. Since 60mg orlistat is now available as an over-the-counter medication, the primary objective of this study was to determine whether 60mg orlistat is as effective a weight loss option in a free living community population with minimal professional input.

Methods: Adipose tissue and ectopic lipid content were measured using MRI and ¹H MR Spectroscopy (MRS), respectively, in 27 subjects following 3 months treatment with orlistat 60mg and a reduced calorie, low-fat diet.

Results: Significant reductions in intra-abdominal AT (-10.6%, p=0.023) subcutaneous (-11.7% p<0.0001) and pericardial fat (-9.8%, p=0.034) volumes and intra-hepatocellular lipids (IHCL) (-43.3%, p=0.0003) were observed. These changes in body fat content and distribution were accompanied by improvements in plasma lipids and decreases in blood pressure and heart rate.

Conclusion: These findings suggest that over-the-counter 60 mg orlistat, in combination with the type of advice a subject could expect to be given when obtaining 60 mg orlistat in a community setting does indeed result in potentially clinically beneficial changes in body composition and risk factors for metabolic diseases.

Clinical Trials: registration number and date 2008-004866-15 (05 Sept 2008)

Key Words:, Magnetic Resonance imaging (MRI), Intra-hepatocellular lipid (IHCL), Adipose tissue, weight loss, Orlistat, visceral fat

Abbreviations: AT: adipose tissue, IAAT: intra-abdominal adipose tissue, ASAT: abdominal subcutaneous adipose tissue, IMAT: inter-muscular adipose tissue, IMCL: intramyocellular lipids, IHCL: Intra-hepatocellular lipid, WC: waist circumference.

Introduction

There is a paucity of prescription drugs available for long-term treatment of obesity. In Europe only Xenical (orlistat 120 mg) is currently licensed. In 2007, orlistat 60mg (alli®) was approved by the FDA as an over-the-counter weight loss medicine. The ability of orlistat 60 mg to significantly reduce body weight has been well-demonstrated (Brochu et al., 2003; Rössner et al., 2000; Anderson et al., 2006; Anderson et al., 2007; Schwartz et al., 2008). Furthermore previous randomized controlled trials have shown that orlistat 120mg can result in beneficial changes in body composition (Tiikkainen et al., 2004; Kelley et al., 2004; Dixon et al., 2007; Chanoine et al., 2005). There is now a need to understand whether orlistat 60mg has a positive impact on weight loss and body composition in a free-living community.

Obesity is currently at epidemic proportions; in 2005 the World Health Organization stated that 1.6 billion adults were overweight worldwide, with 400 million classed as obese. Numbers are predicted to rise to 2.3 billion overweight and 700 million obese by 2015 (WHO, 2006). These levels of obesity are associated with increasing morbidity and mortality connected with diseases including type-2 diabetes, hypertension, dyslipidaemia and non-alcoholic fatty liver disease (NAFLD) (Must et al., 1999).

Risk of developing these chronic conditions is increased in individuals with abdominal obesity. Accumulation of excess intra-abdominal abdominal tissue (IAAT), is a central feature of abdominal obesity. Indeed, elevated IAAT (commonly referred to as visceral fat) and intra-hepatocellular lipid (IHCL) are markers of a dysmetabolic state which increases the risk of type-2 diabetes and coronary artery disease (Després et al., 2008; Fabbrini et al., 2009). The association between IAAT and accelerated atherosclerosis is independent of age, overall obesity or the amount of subcutaneous fat (Hamdy et al., 2006).

It is well known that weight loss results in many health benefits (NIH, 1998). Reductions of 5-10% body weight improve many of the medical complications associated with excess weight (Goldstein, 1992). Many of these benefits are associated with changes in body composition (Hauptman et al., 2000).

Classically, anthropometric measures have been employed to assess body fat distribution. Availability of modern imaging methods for fat quantitation has become a focus of attention particularly in a clinical research setting. Studies using imaging techniques such as magnetic resonance imaging (MRI) have shown that reduction of adipose tissue from key sites known to play a specific pathological role, such as IAAT and IHCL, can result in significant improvements in risk of metabolic and cardiovascular disease (Ross et al., 2004; Thomas et al., 2000).

Our aim was to undertake a pragmatic study to determine whether orlistat 60mg, when given with the minimal professional input, as would be encountered in a real community setting, would lead to beneficial changes in body composition, specifically reductions in IAAT and ectopic fat following 12 weeks of treatment in overweight and obese subjects. Both MRI and MRS imaging were used to measure these changes.

Methods

Written informed consent was obtained from all participants. Ethical approval was obtained from The Joint South London and Maudsley and the Institute of Psychiatry NHS Research Ethics Committee (REC 08/H0807/88), London, UK.

Study Population

Subjects were recruited by poster advertising in the local area and the CIC volunteer panel. This strategy proved effective amongst people working in a local prison and police force, partly explaining the bias towards male subjects.

Inclusion and Exclusion criteria

Inclusion criteria was an age range of 18-60 years, BMI 25-34.9 kg/m², and a waist circumference >88 cm (Female) or >102 cm (Male). Subjects were not eligible if they had recent history of weight loss or were taking prescription drugs that affected body weight or metabolism.

Study Design

This was an open label, non-randomized, 12 week study with one screening and 4 study visits. As a non-prescription medication, the design was more similar to an "actual use study", a trial which is usually conducted as part of a non prescription submission in the United States to access appropriate usage (Brass, 2001). In this type of study, there is not a control group. A full physical exam including ECGs and vital signs, medical history review, urine drug screen, alcohol breath test, routine safety laboratory tests and pregnancy test in female subjects were obtained at the screening visit. Anthropometric measurements were collected including waist circumference (WC) and weight (kg) and height (m). Subjects were fasted for 8 hours prior to screening and MR scans.

Diet: At the time the study was conducted, alli had not been approved in Europe. Subjects meeting the inclusion criteria, were provided a 4 week supply of alli (60mg orlistat) along with educational materials included in the US starter kit, and access to the US alli web site. The

aim was to provide subjects with a similar experience to individuals purchasing alli in a real life setting. At the baseline visit, subjects met with a dietician who discussed the diet, highlighting the importance of reducing one's calories and sticking with the recommended fat intake. The dietician also reinforced the importance of keeping a dietary record as a method of understanding change in eating behaviour. This discussion was aimed to reflect a counselling session between a person buying alli over the counter for the first time and a pharmacist. Subjects were instructed to take the medication 3 times daily with each main meal and to take a multivitamin daily at least 2 hours before or after taking 60mg orlistat. Subjects were encouraged to exercise.

Dietary analysis

Dietary assessment was carried out at week 0 and week 12 using a multipass 24 hour recall (Bingham et al., 1997). Dietary recall was analysed using Dietplan 6 (Forestfield Software Ltd, Horsham UK)

At baseline (study visit 1), MR images were obtained for measurement of abdominal subcutaneous (ASAT) and IAAT, as well as pericardial and inter-muscular adipose tissue (IMAT). Liver and soleus muscle lipid content was measured by ¹H MR spectroscopy.

Study visits 2 and 3 were conducted at 4 and 8 weeks, respectively. During these visits the subjects were queried about adverse events, had their weight and WC measured, returned any unused medication, and received another 4 week supply of orlistat 60mg. Any remaining capsules were counted to evaluate compliance with the study medication.

The final visit was at 12 weeks. Post-treatment MRI/MRS scans were conducted. Prior to the scans, the following assessments were completed: physical examination, body weight/height/waist measurement, fasting lipid blood sample, urine pregnancy test (if applicable), and routine safety laboratory tests.

MR Imaging and Spectroscopy.

MRI scanning was carried out on a 3T Siemens Tim Trio scanner (Siemens Healthcare, Erlangen Germany).

MRI for abdominal and pericardial AT content: The torso was imaged using a 6-channel spine array and two 4-channel body array coils. Imaging data was generated using a 3D spoiled gradient echo sequence with partial Fourier acquisitions (VIBE) (Rofsky et al., 1999). The imaging volume consisted of 4 contiguous 3D slabs, where each 48x3.5mm slice slab (1.76x1.76mm voxels) was acquired in a single 15s end-expiration breathhold (repetition time (TR) = 7ms; echo times (TEs) = 2.45, 3.675ms; flip angle=10°; 450mm field-of-view (FOV); 6/8 partial phase/slab Fourier; 75% slice resolution, 33% slice oversampling, GRAPPA factor 2, non-cardiac gated). The most inferior slab was positioned to begin at the pubic symphysis, the slabs covered 67.2cm superior to this, which surpassed the top of the lungs. Two echoes per excitation were set to acquire fat and water signals in-phase and 180° out-of-phase. These plus 3D fieldmaps were used to decompose the signal into fat and water images.

MRI measurement of IMAT: The position of the calf slice at baseline was marked at its thickest point. This was externally measured from the heel when seated with the knee at a 90° angle and was repeated at follow-up. Calf images were taken with a single VIBE volume (32 slices, 260mm FOV) as described above, using a flexible coil wrapped around the calf.

MRI Image Analysis

Fat-only images in the abdomen were manually segmented into three compartments: (IAAT, pericardial adipose tissue, and ASAT). The abdominal area was defined using anatomical landmarks (top of femoral heads to the bottom of right lung) (Thomas et al., 1998). The volume of IAAT measured contains a mixture of visceral, peri-renal and retroperitoneal adipose tissue; since these cannot easily be differentiated on an MR image.

The fat-only image in the calf was segmented and IMAT measured. All images were anonymized and blinded to time point, but not to subject in order to facilitate matching anatomical landmarks, and analysed by Vardis (Vardis Group Inc, London), using SliceOMatic (Tomovision, Montreal, Canada).

¹H MR spectroscopy

¹H MR spectra were obtained from the right lobe of the liver and the soleus muscle using a PRESS sequence with a 20x20x20mm voxel (TR=1500ms, TE=30ms). Spectra were analysed using the AMARES routine of the jMRUI software package (Naressi et al., 2001). For the liver, the ratio fat/water was calculated using the areas under the water and CH₂ lipid resonances, after correcting for T₁ and T₂ relaxation differences (Thomas et al., 2005). For the soleus, the ratio intramyocellular lipid (IMCL) CH₂/creatine was calculated, after correcting for T₁ and T₂ (Rico-Sanz et al., 1999).

Statistical Analysis

The need for data transformation was explored for all endpoints, and log-transformation was applied to MRI / MRS data in order to account for increased variability seen in larger values.

MRI/MRS data were analysed using analyses of covariance (ANCOVA), and results presented as relative (percent) changes from baseline. ANCOVAs were also used to analyse changes in lipids and vital signs. Changes in anthropometric endpoints (measured monthly) were analysed on the natural scale using mixed model repeated measures analyses.

All models accounted for effects of baseline, age and gender, and estimates of mean changes over time were presented with 95% confidence intervals and corresponding p-values. Associations between measurements were investigated by scatter plots and Pearson correlation coefficients.

A number of datasets were not obtained or deemed of sufficient quality to be included in the overall dataset, often relating to patient motion. Decisions were made prior to statistical analyses. **Numbers of subjects included in final analyses are shown in Tables 2 and 3.**

Results

Twenty seven subjects participated in this study; of these, 26 (7 female, 19 male) were exposed to orlistat. Twenty-four subjects completed the study. Most subjects were Caucasian (n=17), the others were Asian (n=5), Afro-Caribbean (n=2) and mixed race (n=2). The mean age of the participants was 39.8 ± 8.7 years (range 22-56 years), with an average BMI of 31.2 ± 2.4 kg/m² (range 23.3-35.6 kg/m²) and average weight of 95.2 ± 13.1 kg (range 73.3-122.5 kg).

Dietary analysis

Dietary analysis is shown in (Table 1). As expected for an obese population there was an underestimate of total energy intake (Department of Health 1991). The estimated energy intake at baseline was 9944±362 kj verses an actual energy intake of 9279.2 ± 334.4 kj (p<0.01). By the end of the study, actual energy intake had reduced to 5158.7 ± 339.8 kj (p<0.01), with significant decreases in protein, fat and carbohydrate intake.

Change in Body Fat Distribution

Following the 3 month intervention, there was a significant reduction in most adipose tissue depots measured (**Table 2** and Figure 1). There was a significant reduction from baseline in IAAT (-11%, p=0.023), ASAT (-12%, p<0.0001), total abdominal fat (-12%, p=0.0001), and pericardial fat (-10%, p=0.034). IMAT did not show any significant reduction.

We also found a highly significant reduction in IHCL (-43%, p=0.0003). There were no changes in soleus-IMCL.

Anthropometry Changes

Significant reductions in body weight (-2.2%, p<0.0001), BMI (-2.2%, p<0.0001) and WC (-2.0%, p<0.0001) were detected by the first follow-up visit at 1 month (Figure 2). Further reductions were observed at both 2 and 3 month time points. Overall there were significant reductions from baseline in BMI (-5.6%, p<0.0001), WC (-4.3%, p<0.0001), and weight (-5.6%, p<0.0001) following the intervention.

Biochemical and Physiological Changes

Significant reductions from baseline were found for total **cholesterol** (-10.5%, $p < 0.0001$), LDL (-13.4%, $p = 0.0002$) and HDL cholesterol (**-5.2%, $p < 0.0178$**) over the 3 month treatment, as shown in **Table 3**. Changes in triglyceride levels were not significant (-5.4%, $p = 0.3$). Improvements in liver function were observed, with a significant reduction in ALT (-19.3%, **$p = 0.0078$**). Reductions in AST were observed, but did not reach significance (-9.0%, $p = 0.056$). There were also significant reductions in heart rate (-8.6%, $p = 0.0027$) and both systolic (-4.8%, $p = 0.0082$) and diastolic (**-6.3%, $p = 0.0003$**) blood pressure.

Correlations between changes in endpoints at 3 months

Changes in IAAT were significantly correlated with changes in weight ($r = 0.68$, $p = 0.0009$), but not change in WC ($r = 0.22$, $p = 0.3583$). Changes in ASAT were significantly correlated with both weight ($r = 0.92$, $p < 0.0001$) and WC ($r = 0.59$, $p = 0.0094$). Changes in IHCL were significantly correlated with changes in weight ($r = 0.68$, $p = 0.0005$) and all adipose tissue depots (IAAT $r = 0.70$, $p = 0.0008$; ASAT $r = 0.72$, $p = 0.0008$; pericardial AT $r = 0.57$, $p = 0.0094$).

Changes in pericardial AT were most strongly correlated to changes in IAAT ($r = 0.88$, $p < 0.0001$). Interestingly, while changes in pericardial AT were correlated with changes in other AT depots and body weight ($r = 0.52$, $p = 0.015$), there was no relationship with changes in WC ($r = -0.04$, $p = 0.88$), or total cholesterol ($r = 0.12$, $p = 0.61$).

A significant relationship was observed between reduction in body weight and changes in blood pressure (systolic $r = 0.40$, $p = 0.050$; diastolic $r = 0.47$, $p = 0.020$) and heart rate ($r = 0.51$, $p = 0.01$). There was no relationship between changes in IAAT and these parameters. Finally, there was a significant correlation between reductions of body weight and LDL cholesterol ($r = 0.55$, $p = 0.0049$) and between decreases in IAAT and HDL cholesterol ($r = 0.61$, $p = 0.0042$).

Drop-outs and adverse effects

Most subjects completed the intervention with only 2 subjects withdrawing from the study. Several subjects reported adverse effects during the intervention, which were mild and most commonly GI-related ($n = 10$, 38%). Consistent with previous orlistat studies, diarrhoea was reported by some subjects ($n = 7$, 27%).

Discussion

Our results show that even with minimal professional input, that would be typical when buying orlistat in an over-the-counter setting, overweight and obese subjects receiving orlistat 60mg for 12 weeks showed significant reductions in IAAT and ASAT. We also found significant reductions in pericardial fat volumes and intrahepatic lipids following treatment with orlistat 60mg. Dietary assessment demonstrated a significant decrease in energy intake with a fall in all macronutrients.

In addition to reductions in body fat depots, following a 12 week intervention we found with orlistat 60mg, a mean 5.6% decrease in weight, a 4.3% reduction in waist circumference, and a 1.7 unit change in BMI. Changes in weight and WC were accompanied by improvements in blood lipids, LFTs, and blood pressure.

These findings are in accordance with previous research demonstrating the efficacy of orlistat 60 mg in reducing body weight and weight-related co-morbidities (Anderson et al., 2006; Anderson et al., 2007). The magnitude of the effects is similar to those reported previously by others. Schwartz et al in an over the counter minimal intervention study of orlistat (60mg) plus written dietary advice on diet and behaviour change reported subjects lost 4.6 ± 0.7 kg (Schwartz et al., 2008). Tiikkainen et al reported that orlistat (120 mg) has a beneficial effect of AT distribution. In their study of 47 women, they showed reductions in both IAAT and SAT in both orlistat and placebo groups, but found the ratio of IAAT to total AT only decreased in the orlistat group, suggesting reduced fat absorption has an additional benefit over weight loss per se (Tiikkainen et al., 2004).

Kelley et al have previously shown reduced IAAT and improved insulin sensitivity in type-2 diabetic subjects following orlistat (120 mg) for 6 months with diet and exercise (Kelley et al., 2004). Interestingly, changes in weight loss and IAAT were not significantly different between orlistat and placebo. Greater reductions in metabolic markers including fasting insulin and plasma free fatty acids and greater improvement in insulin insensitivity were attributed to orlistat. In the present study, we demonstrated improvements in body composition and biomarkers such as LDL-cholesterol with a lower dose orlistat, despite a shorter study duration, in non-diabetic subjects with minimal professional input. In the Kelley

study subjects met with a nutritionist weekly, while in the current study, participants met with a dietician at the beginning and end of the study.

Orlistat 120 mg in combination with diet has been shown to reduce liver fat in patients with type-2 diabetes (Kelley et al., 2004) and non-alcoholic steatohepatitis (NASH) and reduce inflammation and fibrosis in NASH (Hussein et al., 2007). In the present study we found a 43% reduction in IHCL with modest weight loss (5.6% over 3 month's treatment). Considering the key role of IHCL in the development of insulin resistance (Fabbrini et al., 2009), this finding is important and needs further exploration.

We observed a significant reduction in pericardial fat, despite modest weight loss. Previous studies have reported loss of pericardial fat following greater weight loss over a six month period (Iacobellis et al., 2008). This is the first time that changes in pericardial AT have been demonstrated in patients using orlistat. Reductions in pericardial AT were significantly related to changes in body weight, IAAT and IHCL, although there was no relationship with changes in WC and biochemical markers.

Previous studies suggest that some weight loss treatments may preferentially reduce IAAT compared with subcutaneous deposits (Thomas et al., 2000; Chaston et al., 2008; Hamdy et al., 2006). However, the current study found that orlistat combined with diet reduced AT to a similar extent in both internal (IAAT and pericardial) and subcutaneous depots.

We found no significant correlation between changes in IAAT and waist circumference, despite both reducing during the intervention. WC is often reported as an indirect marker of IAAT content. However, it has been suggested that WC is no better a predictor of IAAT than BMI (Oka et al., 2009). Furthermore it has recently been shown that WC acts predominantly as an index of ASAT (Bosy-Westphal et al., 2010), which may in part explain the findings in the current study.

No significant changes were observed in muscular adipose tissue, located as either IMCL or as IMAT. It is possible that changes in these depots may be secondary to reductions in

abdominal AT depots. This would be in keeping with our previous observations of reductions in IAAT, ASAT and IHCL following life-style induced weight loss. Changes in soleus-IMCL appear to follow only in response to greater weight loss (Thomas et al., 2006)..

This study used novel technologies to provide a comprehensive assessment of the effects of orlistat 60 mg on body composition. Since the effects of orlistat (120 mg) on weight loss and body composition are well established, we did not employ a placebo or diet only group. The precise contribution of orlistat 60 mg per se cannot therefore be determined with certainty; however, the weight loss results were consistent with what has been observed in other trials of orlistat 60 mg (Anderson et al., 2006; Anderson et al., 2007). Previous studies have shown that slightly more weight is lost over 12 months with orlistat 120 mg (Brochu et al., 2003; Rössner et al., 2000), however, in the current study 3 months of 60mg orlistat with minimal professional input produced significant weight loss, resulting in a more favourable body fat distribution, specifically reduced IAAT, IHCL and pericardial fat accompanied by potential health benefits improved plasma lipid profiles, and reduced blood pressure.

Conclusions

These findings suggest that over-the-counter 60 mg orlistat, in combination with the type of advice a subject could expect to be given when obtaining 60 mg orlistat in a community setting does indeed result in potentially clinically beneficial changes in body composition and risk factors for metabolic diseases.

Acknowledgements

This study was funded by GlaxoSmithKline, manufacturers of alli®. ELT and JDB also acknowledge funding from the UK MRC and NIHR Biomedical Research Centre.

Disclosure

Makwana, Newbould, Rao, Gambarota, Delafont, Matthews, Berk, Mishra, Schwartz and Beaver are employees of GSK. Bell and Frost have received consultancy fees from GSK. Thomas declares no conflict of interest.

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Table 1: Dietary assessment at week 0 and week 12 using multipass 24 hour recall

	Baseline	Follow-up	p
Energy kJ	9279.2 ± 334.6	5158.7 ± 339.8	0.001
Protein g	94.8 ± 5.3	56.0 ± 5.4	0.001
Fat g	104.4 ± 7.2	44.8 ± 4.3	0.001
CHO g	227.3 ± 13.3	155.7 ± 13.5	0.001

Results presented as mean ± SEM

Table 2: Analysis of Covariance of MRI Endpoints Percent and Absolute Changes at 3 Months

	n	Percent Change	95% CI	Absolute Change*	95% CI	p-value
Intra-abdominal AT (L)	20	-10.6	(-18.6, -1.8)	-0.60	(-1.05, -0.10)	0.0225
Abdominal subcutaneous AT (L)	19	-11.7	(-15.4, -7.8)	-1.01	(-1.33, -0.68)	<0.0001
Total Abdominal AT (L)	19	-12.2	(-16.9, -7.3)	-1.79	(-2.48, -1.07)	0.0001
Pericardial AT (L)	21	-9.8	(-17.9, -0.9)	-0.022	(-0.040, -0.002)	0.0342
Intermuscular AT (cm ²)	21	-2.2	(-12.1, 8.8)	-0.23	(-1.27, 0.92)	0.6648
IHCL	22	-43.3	(-56.7, -25.7)	-1.41	(-1.85, -0.84)	0.0003
IMCL Soleus	18	-9.8	(-28.2, 13.4)	-1.44	(-4.16, 1.97)	0.3500

Note: Analysis accounting for the effects of baseline, age and sex.

*Note: Absolute change estimates back-calculated from % change estimates and baseline geometric mean

Table 3: Analysis of Covariance of Biochemical and Clinical Parameters - Absolute and Percent Changes at 3 Months

	n	Mean Change	95% CI	Percent Change*	95% CI	p-value
Cholesterol (mmol/L)	24	-0.546	(-0.780, -0.311)	-10.5	(-15.0, -6.0)	<0.0001
High Density Lipids (mmol/L)	24	-0.063	(-0.112, -0.013)	-5.2	(-9.4, -1.0)	0.0168
Low Density Lipids (mmol/L)	24	-0.438	(-0.640, -0.235)	-13.4	(-19.7, -7.2)	0.0002
Triglycerides (mmol/L)	24	-0.087	(-0.262, 0.087)	-5.4	(-16.2, 5.4)	0.3074
ALT (IU/L)	24	-7.6	(-12.0, -2.4)	-19.3	(-30.6, -6.1)	0.0078
AST (IU/L)	24	-2.2	(-4.2, 0.0)	-9.0	(-17.2, 0.2)	0.0556
gGT (IU/L)	24	-3.5	(-7.4, 1.1)	-10.1	(-21.6, 3.1)	0.1230
Systolic Blood Pressure (mmHg)	24	-6.04	(-10.33, -1.75)	-4.8	(-8.2, -1.4)	0.0082
Diastolic Blood Pressure (mmHg/L)	24	-4.92	(-7.25, -2.59)	-6.3	(-9.3, -3.3)	0.0003
Heart Rate (beats/min)	24	-5.46	(-8.78, -2.14)	-8.6	(-13.8, -3.3)	0.0027

Analysis accounting for the effects of baseline, visit, baseline*visit interaction, age and sex.

Percent change estimates back-calculated from absolute change estimates and baseline mean.

Where AST: Serum aspartate aminotransferase; ALT: Alanine aminotransferase; γGT: Gamma-glutamyl transpeptidase.

Figure Legends

Figure 1: Plots showing percent changes in adipose tissue depots following 3 months treatment with orlistat 60mg. († = $p < 0.05$, * = $p < 0.001$) Where IAAT: intra-abdominal adipose tissue, ASAT: abdominal subcutaneous adipose tissue, IMAT: inter-muscular adipose tissue.

Figure 2: Plots showing mean change \pm SEM from initial body weight and waist circumference during 3 months of treatment with orlistat 60mg.

Figure 1.

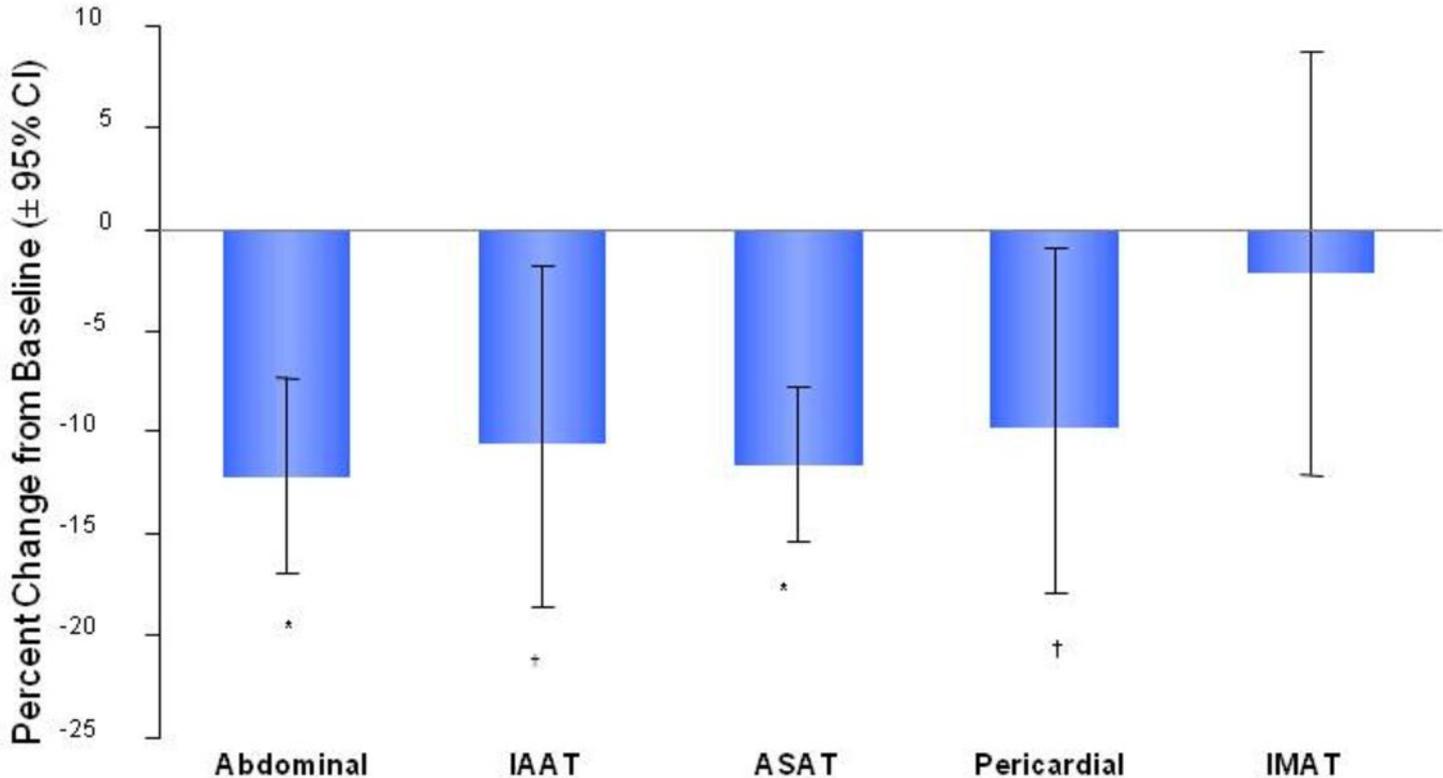
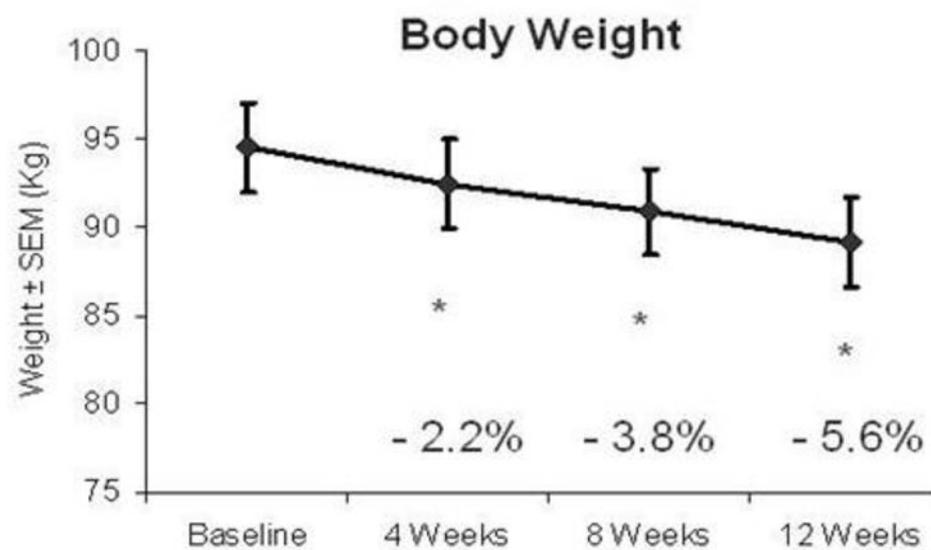
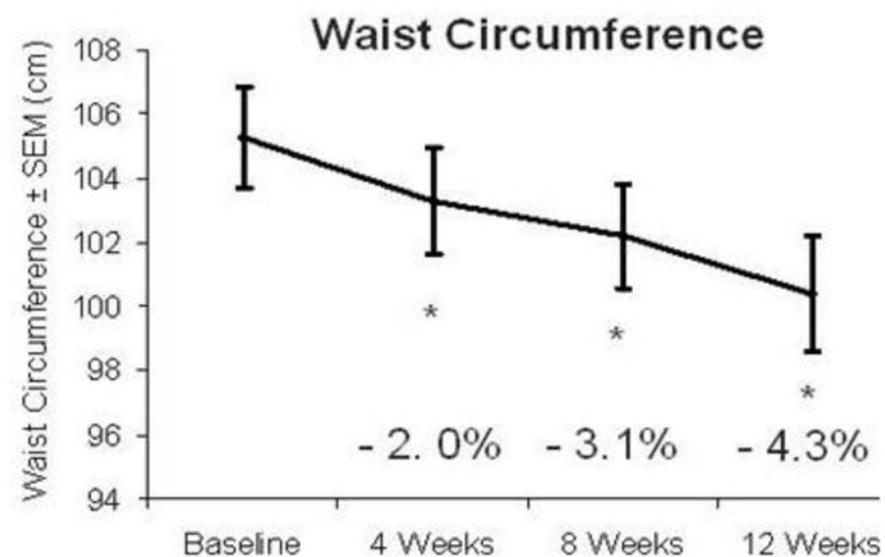


Figure 2



Mean change from baseline to week 12 (kg) = 5.24

* P < 0.001 compared to baseline



Mean change from baseline to week 12 (cm) = 4.54.

* P < 0.001 compared to baseline