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Authors

Tuccinardi, Dario
Farr, Olivia M
Upadhyay, Jagriti
et al.

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Lorcaserin treatment decreases body weight and improves cardiometabolic risk factors of obese adults: A 6-month-long, randomized, placebo-controlled, double-blind clinical trial.

Dario Tuccinardi[†,1], **Olivia M. Farr**[†,1], **Jagriti Upadhyay**[1], **Sabrina M. Oussaada**[1], **Hannah Mathew**[1], **Stavroula A. Paschou**[1], **Nikolaos Perakakis**[1], **Anastasia Koniaris**[1], **Theodoros Kelesidis**[2], and **Christos S. Mantzoros**[1,*]

[1]Division of Endocrinology, Diabetes and Metabolism, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, Massachusetts 02215, USA

[2]Department of Medicine, Division of Infectious Diseases, UCLA David Geffen School of Medicine, Los Angeles, CA, USA

Abstract

Lorcaserin is a serotonin 2c receptor agonist, which promotes weight loss while improving type 2 diabetes and atherogenic lipid profile without higher rates of major cardiovascular events. The full spectrum of the possible lorcaserin-induced cardiometabolic improvements remains to be clarified. Thus, we investigated how lorcaserin administration may alter cardiovascular disease risk, either independently or through changes in body weight, measuring, for the first time, lipid particle quantification, lipid peroxidation, appetite-regulating hormones and the mRNA expression of *5-HT2C receptor*. Forty-eight obese subjects were enrolled in this 6-month-long, randomized (1:1), placebo-controlled, double-blinded clinical trial. Lorcaserin treatment reduced fat mass ($p<.001$), the Fatty Liver Index ($p<.0001$) and energy intake ($p<.03$) without affecting energy expenditure or lean mass. Total low-density lipoprotein (LDL; $p<.04$) and small LDL particles ($p<.03$) decreased, while total high-density lipoprotein (HDL; $p<.02$) increased and heart rate significantly decreased with lorcaserin. No mRNA expression of the *5-HT2C receptor* was observed in peripheral organs. These data suggest that lorcaserin treatment for 6 months improves cardiometabolic health mainly acting through the brain in obese subjects.

Keywords

Obesity; cardiovascular disease risk; lorcaserin; weight loss

[*]**Address Correspondence to:** Christos Mantzoros, MD DSc PhD *hc mult,* 330 Brookline Ave, ST820, Boston, MA 02215, P: 617-667-8630, ofarr@bidmc.harvard.edu.

[†]These authors contributed equally to this work,

Conflicts of Interest

All authors have no conflicts of interest to declare.

Introduction

Obesity and its comorbidities are a global epidemic that increase the risk of cardiometabolic disease[1] and, similar to other chronic conditions, require treatment. Even a modest reduction in weight can lead to improvements in the cardiovascular disease (CVD) risk profile[2]. However, despite the positive effect on weight, pharmacotherapy has often been challenging due to issues related to cardiovascular safety[3]. Conversely, lorcaserin, a Food and Drug Administration (FDA)-approved serotonin 5-hydroxytryptamine 2c (5-HT2c) receptor agonist, effective for long-term weight management[4, 5], recently demonstrated to be also safe, showing no increase in cardiovascular events in addition to improving type 2 diabetes[6, 7].

Although large clinical trials showed an early weight-independent plasma glucose reduction[8] and improvement of CVD risk factors[4, 5] using lorcaserin, no studies have investigated whether lorcaserin acts independently and/or interacts with peripheral signals (e.g., circulating hormones or direct binding with 5-HT2c peripheral receptors) and whether this may affect energy homeostasis, glucose, and lipid metabolism that in turn could improve CVD risk profile.

We have shown that lorcaserin exerts its weight loss effects by reducing brain activations related to attention and emotion in response to food cues[9]. Herein, we extend our previous findings through the same double-blinded, randomized, placebo-controlled trial of lorcaserin (10mg twice a day) vs. matched placebo for 6 months. We examined whether lorcaserin administration either independently or through changes in body weight and fat mass might have 1) modified circulating hormones related to energy homeostasis, 2) altered CVD risk and/or 3) improved non-alcoholic fatty liver disease (NAFLD), by investigating lipid fractionation/peroxidation, changes in the fatty liver index and mRNA expression of *5-HT2C receptor* in an array of human tissues.

Methods

48 participants consented to take part in this randomized (1:1), placebo-controlled, double-blind study, approved by the Institutional Review Board at BIDMC. Patients enrolled after a screening visit (Supplementary Figure 1). Details of methods and inclusion/exclusion criteria are found in our previous publication[9]. Briefly, subjects participated in four study visits during the first month with follow-up visits once a month for 5 additional months. Sample size was estimated as previously described[9]. Plasma and serum were isolated and stored at −80 °C until assayed in duplicate for subsequent analysis (see supplementary methods). HTR2C expression in human tissues was examined using TissueScan quantitative polymerase chain reaction (Qpcr) Arrays (id: TSC10511-HMRT303, OriGene, Rockville, MD, USA; see supplementary methods).

Statistical analysis

SPSS 19 software was used to analyze data. Continuous data are presented as mean ± standard error (SE) unless otherwise indicated. A modified intention-to-treat analysis (mITT) with last observation carried forward (LOCF) was performed with the

anthropometric data to confirm on-treatment analysis. A general linear mixed model, with terms for treatment, time, time*treatment interaction, age, gender and baseline values included as covariates was used to analyze continuous endpoints. The time*treatment interaction statistics were used to determine differences between lorcaserin and placebo. Further adjustments for BMI, fat mass, and concomitant medications were performed to analyze blood pressure, metabolic and lipid measurements (for more specific see supplementary methods).

Results

Demographics and safety

Baseline characteristics of the two randomized groups (n=48) were similar for age (placebo: 49.4±2.7years; lorcaserin: 45.5±3.0years; p<.34) and gender (11 females in placebo vs. 14 in lorcaserin; p<.39), but differed by BMI (placebo: 34.5±0.78kg/m^2; lorcaserin: 40.2±1.5kg/m^2; p<.001). We thus adjusted for baseline BMI in subsequent analyses. No significant differences in potential side effects or safety hormone labs were found. (Supplementary Table 1; Supplementary Table 2).

Anthropometrics and body composition

Participants treated with lorcaserin lost significantly more weight than placebo (−6.25 ± 2.94% vs. 0.06 ± 0.65%. *P*<.001), and the resultant placebo-subtracted weight loss was −7.2kg (*P*<.01; Supplementary Figure 2*A*). The same pattern was observed in the mITT (LOCF) analysis (−4.66 ± 1.36 % vs. −0.09 ± 0.39 %. *P*<.001; Supplementary Figure 2*C*; Supplementary Table 3).

Lorcaserin treatment significantly reduced total body and trunk fat mass (*P*<.001) while body and trunk lean mass were not significantly changed. Similarly, patients treated with lorcaserin exhibited a greater percent reduction in waist circumference than placebo (−3.93 ± 3.28 % vs. 2.56 ± 1.01%. *P*<.001) for a placebo-subtracted reduction in waist circumference of −2.4cm (*P*<.002; Supplementary Figure 2*B*). A similar trend was found in the mITT (LOCF) analysis (−2.73 ± 1.33 % vs. 1.93 ± 0.81 %. P<.005) (Supplementary Figure 2*D*; Supplementary Table 3).

Energy intake and expenditure

Energy expenditure did not change across treatment period, while overall energy intake was reduced (p<.03) without changes in food preference (Table 1).

Metabolic effects

Leptin levels were reduced with lorcaserin treatment (*P*<.05; Table 2), but the difference disappears when corrected for BMI (*P*=.06) or fat mass changes (*P*=.15). No differences in other measured hormones were observed (Table 2). Patients on lorcaserin showed improvements in lipid parameters, including reduction in total cholesterol (*P*<.04), LDL (*P*<.04), and particularly from the lipid subfractionation analysis, in small LDL particles (*P*<.01), oxidized LDL (*P*<.03), VLDL & Chylomicron Particles (*P*<.02) as well as an increase in HDL (*P*<.02), HDL particles (P<.03), large HDL particles (*P*<.04), HDL mean size (*P*<.008)

and ApoA1 (P <.03; Table 2). The Lipoprotein Insulin Resistance Score (LI-IR), an NMR lipid analysis based and validated method to assess insulin resistance, was significantly reduced in the lorcaserin group (P <.05; Table 2). Fatty Liver Index (FLI) decreased in the lorcaserin group (P<.0001; Table 2). All of the above persist after adjustments for BMI, gender, concomitant medication, and age. No changes in blood pressure were detected between the two arms while heart rate significantly decreased in the lorcaserin group (P <. 03; Supplementary Table 1).

Distribution of 5-HT2C receptor mRNA gene expression in human tissues

5-HT2C receptor expression was high in the nervous system (brain, optic nerve, spinal cord). No expression was observed in metabolic organs, such as the liver, pancreas or adipose tissue. In the brain, the *5-HT2C receptor* was highly expressed in choroid plexus, olfactory bulb, substantia nigra, caudate, hippocampus and medulla (Supplementary Figure 3). All analyzed samples were drug-naïve.

Discussion

This study provides novel information on how lorcaserin may alter cardiometabolic risk improving lipid profile and exerting its weight loss effect through decreased appetite. Additionally, we demonstrated potential improvements on NAFLD using a validated index.

Changes in CVD risk

While previous studies have explored changes in lipids with lorcaserin[4, 5], no studies have yet looked at how lipid subfractionation and lipid peroxidation may be altered. Herein, we have shown that independent markers of CVD risk, including waist circumference, total cholesterol, triglycerides, LDL and especially small LDL, significantly decreased after 6 months of lorcaserin treatment. Small LDL particles are more atherogenic than large ones and oxidation increases LDL atherogenicity[10]. We found a significant reduction in small LDL particles that was also accompanied by oxidized LDL percentage change decrease, suggesting benefits of lorcaserin on the LDL profile.

Previous studies have shown that decreased concentrations of HDL particles can predict CVD even more than HDL cholesterol itself and that there is an inverse correlation between CVD and large HDL circulation levels, while the opposite correlation has been observed with small HDL level[11]. HDL size has also been inversely correlated with CVD risk[12]. Herein, we showed a significant increase of HDL and ApoA1 as previously described in a larger clinical trial[4], but also an increase of total HDL particles, large HDL particle concentration and HDL size. We also observed a significant reduction in VLDL and chylomicron particles, which are independently CVD risk factors[13] in the lorcaserin-treated group.

We demonstrate herein an improvement not only of the standard lipid profile but also, for the first time, of the NMR-analyzed lipoprotein sub-particles with lorcaserin. While HDL and LDL related measurements are not affected by fat mass changes, improvements in triglycerides, total VLDL/chylomicron and oxidized LDL with lorcaserin became non-

significant when controlling for fat mass loss, suggesting these changes were fat mass dependent.

Changes in NAFLD risk

We showed herein that patients treated with lorcaserin have a significant reduction of the FLI, which remains after adjusting for fat mass, waist circumference and BMI change, suggesting that lorcaserin may represent an effective treatment for NAFLD or NASH.

Mechanisms of lorcaserin (central vs. peripheral action)

We measured several appetite-related hormones to evaluate the presence of a lorcaserin-endocrine-induced effect in the periphery. We also assessed the mRNA expression of 5-HT2c receptors in the brain as well as in 48 human tissues array normalized to brain expression to investigate a possible direct effect of lorcaserin in the periphery. Hormones involved in appetite control (e.g. leptin) decreased with weight loss in the lorcaserin group, but this association disappeared when controlling for fat mass loss, suggesting these changes were counter-regulatory in function.

The virtual absence of peripheral 5-HT2c receptors and the well-established central action of lorcaserin[9, 14] suggest that lorcaserin exerts its weight loss and metabolic effects primarily within the brain in humans, reducing appetite. Along these lines, we observed no major changes in appetite-regulating hormones between the two groups, confirming a lack of a peripheral effect of lorcaserin. We also observed a significantly reduced caloric intake with no change in resting energy expenditure or RQ with lorcaserin. Altogether, our findings suggest that lorcaserin exerts its weight loss effects through a central mechanism to decrease caloric intake. Notably, the absence of a strong, lorcaserin-induced hormonal peripheral response suggests the opportunity for future combination therapies for weight loss with hormonal agents.

Limitations and Conclusions

The main limitation of this study is the relatively small number of participants, although this was based on *a priori* power calculations and indeed led to statistically significant results. Additionally, we have examined several variables, which were each treated as discrete hypotheses. Despite the small number of participants we confirmed the results of prior studies on weight and lipids outcomes, in a similar population[15]. Retention rate was low, possibly because of the moderate effect in weight loss in both groups. Despite the randomization process, differences in BMI between the two arms at baseline were not fully eliminated. Nevertheless, we have appropriately controlled for this difference in the statistical analyses of the results. A potential limitation of the food diaries is in patient error; however, dieticians reviewed the diaries with patients at each visit and potential errors should be similar in both groups.

We report that lorcaserin-treated patients, in addition to central adipose tissue reduction, showed significant changes in atherogenic lipoproteins that strongly correlate with improved CVD risk, accompanied by a reduction of the FLI. These findings suggest that lorcaserin may represent an effective treatment for CVD risk reduction in obese subjects. However,

considering the exploratory nature of our work and the lack of a clear mechanistic explanation of the metabolic effects observed in subjects using lorcaserin, future studies designed to assess a lorcaserin-induced reduction of CVD events over time will be required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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O.M.F. and C.S.M. designed the experiment. O.M.F., D.T., J.U., H.M., S.A.P., and C.S.M. conducted the trial and acquired data. D.T., S.A.P. and N.P. conducted assays and qPCR. D.T and O.M.F. analyzed the data. D.T. and O. M.F. wrote the manuscript with input from all of the other authors, and D.T. is the guarantor of this article and, as such, takes responsibility for the work as whole. C.S.M. oversaw the entire study, including the study design, evaluation of data and the decision to submit and publish the manuscript.

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Abbreviations:

5-HT2c	5-hypoxytryptamine 2c
Alpha-MSH	Alpha-Melanocyte Stimulating Hormone
BIDMC	Beth Israel Deaconess Medical Center
BMI	body mass index
CRC	clinical research center
CVD	cardiovascular disease
FDA	food and drug administration
FGF-21	fibroblast growth factor 21
FLI	Fatty Liver Index
GH	growth hormone
GIP	gastric inhibitory polypeptide
GLP-1	glucagon-like peptide-1
HDL	high density lipoprotein
HOMA-IR	homeostatic model of insulin resistance
IDL	Intermediate Density Lipoproteins

IGF-1	insulin-like growth factor-1
IGFBP3	Insulin-like growth factor-binding protein 3
LDL	low density lipoprotein
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NMR	nuclear magnetic resonance
oxHDL	Oxidized High Density Lipoprotein
oxLDL	oxidized Low Density Lipoprotein
PYY	peptide YY
VLDL	Very Low Density Lipoprotein

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Table 1.

Anthropometric, body composition, energy expenditure and blood pressure, and heart rate results from study visits over 6 months of lorcaserin or placebo treatment.

	Placebo						Lorcaserin						*p*
Timing	**Baseline**			**Month 6**			**Baseline**			**Month 6**			
Anthropometry													
BMI (kg/m^2)	34.5	±	0.78	34.08	±	0.7	40.2	±	1.5	38	±	3.4	**<.001** *
Body weight (kg)	100.5	±	2.8	99.5	±	2.3	113.5	±	4.7	105.3	±	9.3	**<.001** *
WC (cm)	114.6	±	1.87	113.3	±	1.1	125.7	±	3.56	122	±	6.59	**<.001** *
HC (cm)	118.6	±	2.21	117.8	±	1.89	128.2	±	3.33	120.8	±	6.62	**.01** *
Waist/Hip Ratio	0.97	±	0.02	0.98	±	0.02	0.98	±	0.02	0.98	±	0.04	.26
SBP (mmHg)	126.1	±	2.39	125.2	±	3.16	124	±	3.57	125.6	±	4.48	.51
DBP (mmHg)	75.36	±	2.03	75.25	±	2.04	74.89	±	2.75	77.29	±	2.84	.58
Heart rate (beats/minute)	73.77	±	2.35	76.08	±	2.75	84.94	±	2.53	78.29	±	3.9	**.03** *
Body Composition													
Fat body mass (kg)	38.26	±	2.81	36.86	±	1.71	48.39	±	30.3	44.43	±	64.9	**<.001** *
Fat (% of body mass)	36.38	±	1.87	36.93	±	1.91	41.51	±	1.46	40.7	±	2.84	**<.001** *
Lean body mass (kg)	62.53	±	2.65	62.39	±	1.47	63.07	±	27.1	58.93	±	3.33	.98
Trunk fat mass (kg)	19.4	±	1.1	18.47	±	0.73	23.43	±	1.56	22.45	±	36.4	**<.001** *
Trunk lean mass (kg)	32.39	±	1.47	31.03	±	14.9	32.03	±	1.13	30.93	±	1.63	.56
Total body BMD (g/cm^2)	1.24	±	0.02	1.19	±	0.03	1.21	±	0.03	1.18	±	0.04	.42
Total body T-score	0.68	±	0.25	0.31	±	0.35	0.39	±	0.27	0.24	±	0.31	.31
Caloric Intake and Energy Expenditure													
Caloric intake (kcal)	1954	±	192	2217	±	202	2014	±	252	1864	±	183	**.03** *
% from fat	37.64	±	1.41	33.81	±	1.18	39.49	±	1.59	38.14	±	3.19	.42
% from carbohydrates	43.51	±	1.83	46.82	±	2.95	41.39	±	2.26	42.44	±	4.41	.25
% from proteins	17.48	±	0.87	17.48	±	0.98	18.49	±	1.31	18.25	±	2.06	.61
VO_2 (L/min)	0.24	±	0.01	0.26	±	0.01	0.25	±	0.01	0.24	±	0.01	.06
VO_2/Kg (ml/kg/min)	2.5	±	0.08	2.62	±	0.13	2.3	±	0.07	2.34	±	0.11	.84
VCO_2 (L/min)	0.21	±	0.01	0.02	±	0.01	0.21	±	0.01	0.19	±	0.01	.55
RQ	0.83	±	0.08	0.79	±	0.01	0.82	±	0.01	0.78	±	0.03	.61
REE (kcal/day)	1697	±	64	1792	±	114	1772	±	71	1663	±	103	.27
BMR (kcal/day)	1859	±	62	1833	±	78	1933	±	74	1805	±	116	.12

Data shown as means ± standard error (SE) of the mean from an on-treatment analysis. Patients included as long as they attended at least two visits. Weight, waist and hip circumferences and blood pressure measurements were analyzed across weeks 0, 1, 2, 4, and months 2, 3, 4, 5, while DEXA body composition and energy expenditure were analyzed across months 0, 1 and 6. Caloric intake was analyzed across week 0, 4 and month 3 and 6. The P-value was from a general linear mixed model analysis of the parameters. The variables of time, treatment and time*treatment were included in the model as fixed effects. Gender and age were included as covariates. The P-value time*treatment interaction is shown. The P-value for treatment is shown only for caloric intake.

* P <0.05. WC, waist circumference; VAT, visceral adipose tissue; RQ, respiratory quotient; REE, resting energy expenditure; BMR predicted basal metabolic rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2.

Metabolic, hormonal, lipids and nuclear magnetic resonance (NMR)-derived lipid particle concentrations from study visits over six months of lorcaserin or placebo treatments.

	Placebo						Lorcaserin						*p*
Timing	**Baseline**			**Month 6**			**Baseline**			**Month 6**			
Glucose (mg/dL)	92.18	±	1.76	94.41	±	2.25	93.28	±	2.08	95.71	±	3.02	.75
HbA1c (%)	5.86	±	0.59	5.82	±	0.87	5.75	±	0.71	5.85	±	0.78	.84
C-peptide (ng/mL)	2.65	±	0.35	2.81	±	0.46	2.98	±	0.34	2.97	±	0.33	.18
HOMA-IR	3.64	±	0.49	2.72	±	0.43	3.91	±	0.37	3.32	±	0.56	.22
Lipoprotein Insulin Resistance Score	55.63	±	5.01	50.09	±	5.43	49.28	±	3.28	39.71	±	3.59	**.05** *
FLI	79.95		5.03	81.62	±	3.35	90.48		2.98	79.93	±	8.66	**<.0001**
Alpha-MSH (pmol/L)	17.41	±	2.07	23.65		3.61	21.91		1.61	17.95		4.52	.42
GH (ng/mL)	0.66	±	0.24	1.41	±	0.71	0.81	±	0.21	0.32	±	0.11	1.3
IGF-1 (ng/mL)	130	±	13.62	120	±	14.81	137.5	±	17.68	112.7	±	16.58	.95
IGFBP3 (ng/mL)	4.9	±	0.32	5.31	±	0.49	5.69	±	0.56	5.86	±	0.95	.27
Cortisol (ug/dL)	16.27	±	1.62	12.54	±	1.98	16.91	±	1.21	11.71	±	1.97	.49
FGF-21 (pg/mL)	222.47	±	24.89	223.25	±	43.59	268.84	±	57.72	331.50	±	77.56	.65
Leptin (pg/mL)	33.02	±	4.24	27.39	±	4.31	57.2	±	6.01	38.98	±	8.56	**.05** *
Adiponectin (pg/mL)	14.63	±	1.99	17.09	±	2.3	12.67	±	1.35	17.71	±	1.91	.9
Ghrelin (pg/mL)	513.62	±	54.55	584.44	±	28.79	484.97	±	39.82	580.38	±	26.01	.84
PYY (pg/mL)	94.26	±	9.23	83.21	±	12.81	83.85	±	5.94	76.86	±	5.83	1.6
GLP-1(pg/mL)	43.90	±	3.94	29.07	±	5.42	40.32	±	4.46	27.77	±	3.93	.61
Oxyntomodulin (pg/mL)	387.78	±	67.94	161.64	±	30.45	401.86	±	57.41	213.67	±	16.89	.17
Regular Lipids													
Total cholesterol (mg/dL)	181.2	±	7.36	185.8	±	6.51	177.3	±	7.12	174.7	±	15.5	**.04** *
Triglycerides (mg/dL)	122.51	±	8.96	102.4	±	11.85	117.7	±	8.85	96.43	±	12.9	**<.001** *
LDL cholesterol (mg/dL)	102.7	±	6.23	106.7	±	5.81	106.8	±	5.45	99.29	±	12.6	**.03** *
Non-HDL cholesterol (mg/dL)	127.2	±	6.67	129.6	±	5.57	130.2	±	6.51	118.4	±	14.5	**.02** *
HDL cholesterol (mg/dL)	52.58	±	3.37	53.67	±	3.49	47.06	±	2.19	56.29	±	4.46	**.031** *
ApoA1 (mg/dL)	150.4	±	6.11	150.9	±	5.45	138.1	±	4.86	148	±	10.2	**.03** *
ApoB (mg/dL)	90.48	±	3.81	86.61	±	4.89	88.01	±	5.01	88.29	±	8.85	.39
NMR Analyis													
VLDL and Triglycerides													
Total VLDL & chylomicron particles (nmol/L)	51.83	±	4.62	41.33	±	5.45	55.39	±	4.57	42.02	±	9.05	**.02** *
Low Density Lipoproteins													
Small LDL particles (nmol/L)	370.4	±	32.5	465.5	±	41.4	410.1	±	25.5	399	±	66.3	**.01** *
oxLDL	318.1	±	21.3	353.7	±	29	372.1	±	28.5	360.4	±	26.4	.05
oxLDL % change				14.91	±	2.98				−2.47	±	4.13	**.03** *
oxLDL/LDL	3.35	±	0.23	3.68	±	0.31	3.5	±	0.23	3.9	±	0.42	.23
High Density Lipoproteins													

	Placebo						Lorcaserin						*p*
Timing	**Baseline**			**Month 6**			**Baseline**			**Month 6**			
HDL particles (μmol/L)	29.03	±	1.29	29.46	±	1.32	28.51	±	1.57	31.54	±	2.43	**.03** *
HDL cholesterol (mg/dL)	42.01	±	3.34	42.64	±	2.31	42.22	±	2.61	53.57	±	5.84	**.02** *
Large HDL particles (μmol/L)	4.31	±	0.66	4.39	±	0.53	4.57	±	0.46	6.95	±	0.99	**.04** *
HDL size (nm)	8.97	±	0.13	9.06	±	0.12	9.16	±	0.09	9.67	±	0.16	**<.008** *
Clusterin (μg/mL)	33.12	±	1.53	31.23	±	1.72	33.51	±	1.82	30.31	±	1.99	.53
Clusterin %change	0			−8.41	±	6.79	0			3.37	±	13	.77
oxHDL	0.66	±	0.04	0.6	±	0.04	0.69	±	0.03	0.59	±	0.05	.59
oxHDL%change	0			−2.7	±	4.31	0			−1.5	±	6.32	.29
LIRS	55.63	±	5.01	50.09	±	5.43	49.28	±	3.28	39.71	±	3.59	**.05** *

Data shown as means ± standard error (SE) of the mean from an on-treatment analysis. Patients included as long as they attended at least two visits. Hormonal measurements took place at weeks 0, 1, 2, 4, and months 3 and 6; Lipid measurements took place at weeks 0, 1, 2, 4, and months 3 and 6; oxLDL and cluserin measurement took place at Months 0, 1 and 6. The p-value is from a general linear mixed model analysis of the parameters. The variables of time, treatment and time*treatment were included in the model as fixed effects, gender, BMI, baseline values and age were included as covariates. The P-value time*treatment interaction is shown

* P <0.05; HOMA-IR, homeostatic model of insulin resistance; PYY, peptide YY; GLP-1, glucagon-like peptide-1; GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP3, Insulin-like growth factor-binding protein 3; GIP, gastric inhibitory polypeptide; FGF-21, fibroblast growth factor 21; FLI, Fatty Liver Index; VLDL, Very Low Density Lipoprotein; LDL, Low Density Lipoprotein; IDL, Intermediate Density Lipoproteins; HDL, High Density Lipoprotein; oxLDL, oxidized Low Density Lipoprotein; oxHDL, oxidized High Density Lipoprotein; LIRS, Lipoprotein Insulin Resistant Score