Clinical Study

Impact of Orlistat-Induced Weight Loss on Diastolic Function and Heart Rate Variability in Severely Obese Subjects with Diabetes

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Objective. Determine the impact of Orlistat-induced weight loss on metabolic profile and cardiovascular function in severely obese patients with type 2 diabetes. *Methods*. Twenty-nine patients were randomized either to a nonplacebo control group or to a treatment group with Orlistat thrice a day. Metabolic profile, anthropometric parameters, heart rate variability indices, and echocardiographic variables were measured before and after a 12-week treatment period. *Results*. Treatment with Orlistat induced a modest but significant weight loss compared to controls (3.7 ± 3.0 versus 0.5 ± 2.2 kg, resp.; $P = .003$). There was significant decrease in fasting glycemia (7.9 ± 3.0 versus 6.7 ± 2.2 mmol/L; $P = .03$) and significant improvements in left ventricular diastolic function ($P = .03$) and in the sympathovagal balance (LF/HF ratio) ($P = .04$) in the Orlistat group. *Conclusion*. These results suggest that a modest weight loss improves fasting glycemia, left ventricular diastolic function, and sympathovagal balance in severely obese patients with type 2 diabetes.

1. Introduction

Severe obesity is defined as a body mass index (BMI) >40 kg/m^2 which is associated with comorbidities such as insulin resistance, diabetes mellitus, systemic hypertension, dyslipidemia, and cancer. Obesity is an independent risk factor for increased cardiovascular morbidity and mortality [1]. Furthermore, severely obese subjects have an increased total mortality with a concomitant increased risk of sudden death, which may be caused by fatal arrhythmias [1].

Heart rate variability (HRV) which is the fluctuation of heart rate around mean heart rate that may be assessed with a 24-hour cardiac Holter monitoring provides valuable information on the activity of the cardiac autonomic nervous system (ANS). The ANS is an important contributor to the regulation of both the cardiovascular system and energy expenditure and it is assumed to play a role in the pathophysiology of obesity and related complications [1, 2]. In obese subjects, many studies have observed abnormalities in the sympathetic and the parasympathetic ANS activity, which could partly explain the relation between obesity, comorbidities, sudden death, and arrhythmias [1, 3]. Available data regarding the metabolic and ANS impacts of weight loss in severely obese subjects by other methods than gastric bypass [4, 5] and hypocaloric diet [3, 6–9] are sparse.

Excess body fat also directly influences heart function [1]. Obesity is associated with decreased left ventricular (LV) systolic function and impaired LV diastolic function [1, 10]. Whereas some studies using surgical procedures have reported that substantial weight loss induces significant improvements in LV diastolic function [10–14], the effect of modest weight loss on LV diastolic dysfunction in obese subjects has been less extensively investigated but has never been reported in severe obesity. Diet and exercise programs are associated with disappointing long-term results on weight loss in severely obese subjects [15]. Weight loss medication is recommended for subjects with a BMI >30 kg/m^2 or with a BMI >27 kg/m^2 associated with ≥ 1 risk factor of cardiovascular disease [16]. Orlistat is a gastrointestinal lipase inhibitor, reducing fat absorption, which may result in weight loss of approximately 5%–10% of the initial weight after one year [17]. It may be relevant to investigate the

impact of modest weight loss on LV diastolic function and on HRV since these parameters may be associated with increased cardiovascular risk [18, 19]. This pilot study aimed to determine the impact of weight loss induced by Orlistat on HRV and on LV diastolic function in severely obese patients with type 2 diabetes.

2. Methods

2.1. Subjects. A total of 38 severely obese patients with type 2 diabetes were recruited from the waiting list of bariatric surgery in our Institution. The experimental protocol was approved by the ethics committee of IUCPQ and we certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. All the subjects gave their written informed consent. Subjects 18 years or older and treated with antidiabetic medication and/or insulin were included. Subjects were excluded if they used medication known to influence HRV or if they had documented chronic heart failure and/or kidney failure. Subjects were randomized to a control group or to a treatment group, which consisted of 120 mg of Orlistat (Xenical Roche, Nutley, NJ, USA) thrice a day, 30 minutes before meal, for 12 weeks. The medication was provided at no cost. For both treated and control groups, no reinforced specific nutritional intervention was recommended during this study other than the usual nutritional advice regarding the medication, reflecting a real clinical context. Follow-up was systematically conducted by phone for all subjects at 4 and 8 weeks into the study, in order to ensure subject's compliance with the medication and to note any significant changes in lifestyle. Nine subjects did not complete the study. In the control group, (1) one underwent bariatric surgery, (2) one had medication change within follow-up period, and (3) five did not attend their follow-up visit. In the treated group, (1) one had clinically significant side effects on the medication, and (2) one did not attend the follow-up visit.

2.2. Anthropometric Measurements. Total body mass, lean and fat mass, height, and BMI have been determined with an electrical bioimpedance balance (Tanita TBF-350, Tokyo, Japan). Waist circumference was measured using standardized method with an inelastic tape. Blood pressure and resting heart rate were measured following a 30-minute resting period while subjects were lying on their side during the echocardiogram study. Blood pressure was measured using an adapted size blood pressure cuff and an electronic sphygmomanometer (Welch-Allyn, 5200 series, Arden, NC, USA).

2.3. Biochemistry. Blood sample was taken after a 12-hour fast. Glycemia was determined using an enzymatic method (Hitachi, 717 Auto analyzer; Roche, Laval, Canada) and glycated hemoglobin (HbA$_{1c}$) was measured by binding affinity (Abbot IMX, Mississauga, Canada). Plasma cholesterol and triglycerides concentrations were measured using previously described methods (Hitachi, 717 Auto analyzer; Roche, Laval, Canada) [20, 21]. Serum HDL-cholesterol was analysed with an enzymatic precipitation of LDL-cholesterol and VLDL-cholesterol, using phosphotungstate and MgCl$_2$. LDL-cholesterol concentration was calculated with Friedewald's formula [22].

2.4. Echocardiography. Echocardiographic measures were performed with a commercial ultrasound system (Sonos 5500; Hewlet Packard, Andover, Massachusetts). Standard parasternal, short-axis, and apical views were performed in accordance with the recommendations of the American Society of Echocardiography and the same observer, who was blinded to randomisation, obtained all recordings and measurements. Left ventricular diastolic dysfunction (LVDD), using transmitral and pulmonary veins recordings, was evaluated using well-standardized criteria as previously reported [20, 21]. Tissue Doppler was not performed.

Left ventricular mass (LVM) was calculated according to the following formula [23]: LVM (g) = $0.8 \times 1.04[(LVEDD + IVST + PWT)^3 - (LVEDD)^3] + 0.6$, where LVEDD represents the left ventricle end diastolic dimension, IVST the interventricular septal thickness, and PWT the posterior wall thickness.

2.5. Heart Rate Variability. Heart rate variability (HRV) was derived from a 24-hour Holter monitoring system (Marquette Electronics Inc., Milwaukee, WI) in all subjects during normal daily life activity [21]. Numerous indices in the frequency and the time domains were determined [7, 21]: mean value of all RR intervals (mean NN), standard deviation of the RR intervals (SDNN), standard deviation of the mean NN intervals for each 5 minutes period (SDANN), square root of the mean squared difference of successive RR intervals (rMSSD), percentage of differences between adjacent normal RR intervals exceeding 50 milliseconds (pNN50), high frequency (HF), and low frequency (LF). Within the 24-hour evaluation, three periods were assessed: (1) 24 hours, (2) daytime period defined as 8:00 AM to 8:00 PM, and (3) night time period defined as 12:00 AM to 6:00 AM. The separation into daytime and night time was arbitrary [7].

2.6. Statistical Analysis. Data are presented as mean ± standard deviation unless otherwise specified. Comparisons between normal, spontaneous, and pseudonormal pattern of LV filling pre and posttreatment were conducted with a mixed ANOVA design. This analysis allowed us to first compare groups (treatment versus control) in regards to baseline data and to determine the treatment effect as well as interactions between groups and treatment. The factor with random effect was linked to subjects. The dependent variable associated to LV diastolic function was analysed using a cumulative multinomial distribution with an independent covariance structure. Thereafter, if significant differences occurred, *a posteriori* Tukey's comparison technique was performed to determine differences. Relationships among variables were measured using Pearson's correlation coefficients. In order to test the normality distribution of the data,

TABLE 1: Baseline characteristics of type 2 diabetic severely obese subjects before and after treatment.

	Control group		Treatment group	
	Pre	Post	Pre	Post
N	13	13	16	16
Age (years)	48 ± 11	—	47 ± 9	—
Duration of diabetes (years)[1,3]	4.8 ± 4.6	—	7.2 ± 6.1	—
Men/Women (number)	7/6	7/6	7/9	7/9
Weight (kg)	142.6 ± 34.6	142.1 ± 35.0	129.6 ± 17.4	125.9 ± 17.5*‡
BMI (kg/m^2)	51.2 ± 9.2	51.2 ± 9.0	45.9 ± 7.3	44.8 ± 7.5*‡
Waist circumference (cm)	145.8 ± 20.8	144.3 ± 20.6	138.4 ± 14.7	133.9 ± 17.0*
Fat percentage (%)[2]	48.5 ± 5.4	48.8 ± 4.1	45.7 ± 8.3	45.6 ± 8.7
Fat mass (kg)[2]	67.3 ± 13.6	66.2 ± 13.8	59.1 ± 13.1	57.4 ± 13.5
Fat free mass (kg)[2]	72.3 ± 18.9	70.0 ± 17.8	70.4 ± 15.4	68.5 ± 15.2*
Resting HR (beat/min)	83 ± 7	84 ± 12	80 ± 12	78 ± 11
SBP (mmHg)	127 ± 20	126 ± 15	137 ± 18	127 ± 13
DBP (mmHg)	71 ± 10	70 ± 9	74 ± 12	70 ± 11
Fasting glycemia (mmol/L)[1,3]	8.0 ± 2.5	8.1 ± 2.5	7.9 ± 3.0	6.7 ± 2.2*
HbA$_{1c}$ (%)[1]	7.3 ± 1.1	6.7 ± 0.9*	7.3 ± 2.1	6.6 ± 1.3*
Total cholesterol[4]	4.8 ± 0.8	4.7 ± 0.7	4.5 ± 0.7	4.3 ± 0.8
HDL-cholesterol (mmol/L)[4]	1.3 ± 0.2	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3
LDL-cholesterol (mmol/L)[4]	2.7 ± 0.8	2.5 ± 0.7*	2.5 ± 0.6	2.2 ± 0.8*
Triglyceride (mmol/L)[4]	1.8 ± 0.5	2.0 ± 0.7	1.7 ± 0.6	1.9 ± 0.8

Mean ± standard deviation; *P < .05: pre versus post; ‡P < .05: control versus treatment; BMI: Body mass index; DBP: Diastolic blood pressure; HR: Heart rate; MBP: Mean blood pressure; SBP: Systolic blood pressure.
[1]One subject missing in the control group.
[2]Two subjects missing in the control group.
[3]One subject missing in the treatment group.
[4]Two subjects missing in the treatment group.

the Shapiro-Wilk test was performed. Brown and Forsythe's variation of Levene's statistics test was used to verify the homogeneity of variances. A P value inferior to .05 was considered statistically significant. Data were analysed using the statistical packages Sigma Stat (Chicago, IL, USA) and SAS (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Clinical Parameters. Table 1 presents clinical characteristics of patients in both groups before and after treatment. There were no significant statistical differences between the two groups for all parameters at the beginning of the study (Table 1). After 3 months of treatment with Orlistat, there was a significant reduction in body weight (P < .001), BMI (P = .003), and waist circumference (P = .005). When compared to the control group, mean weight loss (3.7 ± 3.0 versus 0.5 ± 2.2 kg; P = .003), corresponding to a percentage of weight loss of 2.9 ± 2.5 versus 0.3 ± 1.5% (P = .003), was statistically different. Weight loss in the treatment group was associated with improvements in fasting glycemia, which decreased only in the group treated with Orlistat (P = .03). However, there was a significant decrease in HbA$_{1c}$ (controls: P < .001 and treated: P = .02) as well as in the LDL-cholesterol levels in both groups (controls: P = .05 and treated: P = .03). In the treatment group, fat-free mass decreased significantly (P = .03). No significant difference

was observed between the two groups after treatment for the other anthropometric and metabolic parameters (Table 1).

3.2. Heart Rate Variability

3.2.1. Time Domain. In the 24-hour HRV indices, there was a significant increase in rMSSD (P = .02) as well as in pNN50 (P = .03) in the treated group following weight loss (Table 2). While there was no significant change in the HRV daytime indices, night time measures showed a significant improvement in rMSSD in the treated group only (P = .023).

3.2.2. Spectral domain. Following weight loss, high-frequency (HF) power measured during the 24-hour period increased significantly (P = .05), but during daytime and night time, increments did not reach statistical significance (daytime: P = .056 and night time: P = .1) (Table 2). The LF/HF ratio decreased significantly in the treated group in the 24-hour assessment (P = .038) as well as during daytime (P = .006).

3.3. Echocardiography. Echocardiographic parameters measured in both groups as well as normal values are shown in Table 3. There were no statistically significant differences in heart dimensions or parameters of LV diastolic function between the control group and the Orlistat-treated group at

TABLE 2: Heart rate variability indices in severely obese subjects with type 2 diabetes before and after treatment.

(a) 24 hour

	Control group		Treatment group	
	Pre	Post	Pre	Post
N	13	12	16	16
Mean NN (ms)	768 ± 86	786 ± 111	775 ± 102	796 ± 101
SDNN (ms)	106 ± 34	106 ± 30	102 ± 25	112 ± 23
SDANN (ms)	93 ± 38	91 ± 35	88 ± 22	97 ± 22
rMSSD (ms)	26 ± 15	28 ± 16	24 ± 10	30 ± 10*
pNN50 (%)	7 ± 10	8 ± 10	6 ± 7	9 ± 8*
HF (ln)	4.4 ± 1.0	4.6 ± 0.9	4.5 ± 0.9	4.9 ± 0.7*
LF (ln)	5.6 ± 0.9	5.7 ± 0.7	5.7 ± 1.0	5.9 ± 0.7
LF/HF ratio	3.7 ± 1.9	3.4 ± 1.7	3.3 ± 1.1	2.8 ± 1.3*

(b) Daytime

	Control group		Treatment group	
	Pre	Post	Pre	Post
N	13	12	16	16
Mean NN (ms)	733 ± 100	762 ± 133	734 ± 104	742 ± 105
SDNN (ms)	80 ± 29	85 ± 30	80 ± 22	84 ± 22
SDANN (ms)	68 ± 23	69 ± 26	63 ± 18	66 ± 21
rMSSD (ms)	21 ± 18	26 ± 20	21 ± 8	25 ± 9
pNN50 (%)	5 ± 13	7 ± 13	4 ± 5	6 ± 7
HF (ln)	3.8 ± 1.2	4.3 ± 1.2	4.1 ± 1.0	4.6 ± 0.8
LF (ln)	4.9 ± 0.9	5.4 ± 0.8	5.5 ± 1.0	5.7 ± 0.7
LF/HF ratio	3.8 ± 2.4	3.7 ± 2.5	4.0 ± 1.8	3.2 ± 1.2*

(c) Night time

	Control group		Treatment group	
	Pre	Post	Pre	Post
N	13	12	16	16
Mean NN (ms)	840 ± 86	827 ± 96	851 ± 112	890 ± 105
SDNN (ms)	88 ± 45	86 ± 30	83 ± 25	85 ± 23
SDANN (ms)	57 ± 39	60 ± 31	57 ± 18	53 ± 16
rMSSD (ms)	32 ± 17	30 ± 11	31 ± 15	36 ± 16*
pNN50 (%)	10 ± 12	10 ± 10	11 ± 12	15 ± 14
HF (ln)	5.1 ± 1.1	4.9 ± 0.9	5.0 ± 1.0	5.4 ± 1.0
LF (ln)	6.2 ± 1.1	5.9 ± 0.9	6.0 ± 1.0	6.2 ± 0.9‡
LF/HF ratio	3.7 ± 2.6	3.2 ± 2.0	2.9 ± 1.4	2.6 ± 1.7

Mean ± standard deviation; *$P < .05$: pre versus post; ‡$P < .05$: control versus treatment; ln: logarithmic transformation; HF: High frequency; LF: Low frequency; Mean NN: Mean value of all RR intervals; pNN50: Percentage of intervals differing of ≥50 ms than the preceding interval; rMSSD: square root of the mean squared difference of successive RR intervals; SDANN: Standard deviation of the mean NN intervals for each 5 minutes period; SDNN: Standard deviation of the RR intervals.

the beginning of the study. Despite normal baseline values, we observed a nonstatistical increment in ejection fraction after treatment with Orlistat ($P = .054$), the values after treatment being also significantly greater than the ejection fraction values of the control group ($P = .04$). There were 11 out of 16 subjects with impaired LV diastolic function (7 spontaneous and 4 pseudonormal LVDD) in the treatment group while there were 7 out of 13 subjects (5 spontaneous and 2 pseudonormal LVDD) in the control group (Figure 1). Isovolumetric relaxation time, A wave velocity, E/A ratio, deceleration time, as well as the A wave duration were not statistically different following treatment. However, E wave velocity significantly increased in the treatment group ($P = .046$). During the Valsalva manoeuvre, we observed a significant decrease of the A wave velocity in the treatment group ($P = .007$), concomitant to a significant increase in the E/A ratio ($P = .024$). This increment was statistically different to the effect observed in the control group ($P = .027$). Accordingly, for the patients with a pseudonormal diastolic function, using the E/A value assessed during the

Table 3: Echocardiographic parameters in severely obese subjects with type 2 diabetes before and after treatment.

	Normal values	Control group		Treatment group	
		Pre	Post	Pre	Post
N		13	13	16	16
Aortic root (mm)	20–37	33 ± 4	$35 \pm 4^*$	33 ± 4	$33 \pm 4^{\ddagger}$
IVS (mm)	6–11	11 ± 1^1	11 ± 1^1	11 ± 2^1	11 ± 2
PW (mm)	6–11	10 ± 2^1	10 ± 1^1	11 ± 1^1	$10 \pm 1^*$
LA (mm)	19–40	42 ± 4	41 ± 5	42 ± 4	41 ± 3
RV diastolic (mm)	7–23	26 ± 4	26 ± 4	26 ± 3	26 ± 3
LV diastolic (mm)	35–57	53 ± 8	54 ± 9	50 ± 4	51 ± 3
LV systolic (mm)	20–39	34 ± 9^2	35 ± 10^1	29 ± 4^1	30 ± 4
LV mass (g/m)[4]	M < 163 W < 121	226 ± 74^2	233 ± 61^2	209 ± 53^3	$198 \pm 46^{2*}$
Ejection fraction (%)	>50	60 ± 11	60 ± 13	64 ± 5	67 ± 4

Mean ± standard deviation; $^*P < .05$: pre versus post; $^{\ddagger}P < .05$: control versus treatment; IVS: Interventricular septum; LA: Left atrium; LV: Left ventricle; PW: Posterior wall; RV: Right ventricle.
[1]One missing subject.
[2]Two missing subjects.
[3]Three missing subject.
[4]Normal values: <163 g/m for men and <121 g/m for women [24].

Valsalva manoeuvre in order to account for the increased pressure of LV filling, there was a significantly enhanced LV diastolic function in the treatment group ($P = .014$). There was no difference in the other indices of LV diastolic function.

Figure 1 shows the influence of weight lost on LV diastolic function. Thirty-height percent of the subjects (6/16) in the treatment group significantly improved their LV diastolic function ($P = .03$). In contrast, in the control group, there was no improvement ($P = .35$) except for one subject while 3 subjects worsen their LV diastolic function. The amelioration of LV diastolic function in the treated group was significantly different to the control group ($P = .026$).

3.3.1. Correlations. As expected, a positive correlation was found between body weight and BMI and LV mass ($r = 0.68$ and $r = 0.44$, resp.; both $P < .001$). An inverse correlation was also observed between body weight, BMI, and LV ejection fraction ($r = -0.48$ and $r = -0.52$, resp.; both $P < .001$). There was positive correlation between E/A ratio and 24-hour measurement of HF ($r = 0.361$; $P < .01$), rMSSD ($r = 0.456$; $P < .001$), and pNN50 ($r = 0.458$; $P < .001$). Changes in E/A ratio and delta LF/HF ratio during 24-hour and daytime also showed correlations ($r = 0.377$; $P = .048$ and $r = 0.458$; $P = .014$, resp.).

4. Discussion

We observed that modest Orlistat-induced weight loss enhances sympathovagal balance and cardiac function in severely obese patients with type 2 diabetes. After a 3-month treatment period with Orlistat, subjects lost significantly more weight than subjects in the control group.

Akehi et al. reported that very-low calorie diet-induced weight loss in moderately obese subjects improved NN, SDNN, SDANN, rMSSD, HF, and LF/HF ratio values [6]. This was interpreted as an improvement in the sympatho-vagal balance. Similarly, Poirier et al. [7] reported that a 10% diet-induced weight loss in 8 severely obese subjects was associated with significant improvement in autonomic cardiac modulation through enhancement of parasympathetic modulation which translates clinically into decreased heart rate and increased HRV. In our study, rMSSD, pNN50, and HF values of the 24-hour HRV were significantly improved in the treated group. All these indices are considered to reflect the parasympathetic system and being protective from a cardiovascular disease viewpoint [25]. Furthermore, another significant improvement was the decrease in the LF/HF ratio assessed during 24 hours and during daytime in the treatment group. Accordingly, Poirier et al. observed that the improvement in HRV after weight loss occurred mainly during the daytime period [7]. Our results show similar improvement in the parasympathetic modulation and in the sympathovagal balance, particularly during daytime. Studies [10, 14, 26] reported that, following bariatric surgery which induced important weight loss in severely obese subjects, LV mass was significantly reduced. In our study, weight loss in the treatment group was accompanied with a significant decrease in the posterior wall thickness and in LV mass as also reported by others [27–29].

To our knowledge, there are no data available in severely obese subjects investigating the impact of weight loss on the pseudonormal pattern of LV filling using the Valsalva manoeuvre. We observed an improvement of LV diastolic function in over half of the treated subjects compared to only one patient who had an improved LV diastolic function in the control group. Of note, the relations between HRV and echocardiographic parameters revealed that rMSSD and HF values correlate with E/A ratio. Interestingly, we also found a significant positive correlation between changes in E/A ratio and changes in LF/HF ratio during 24-hour and
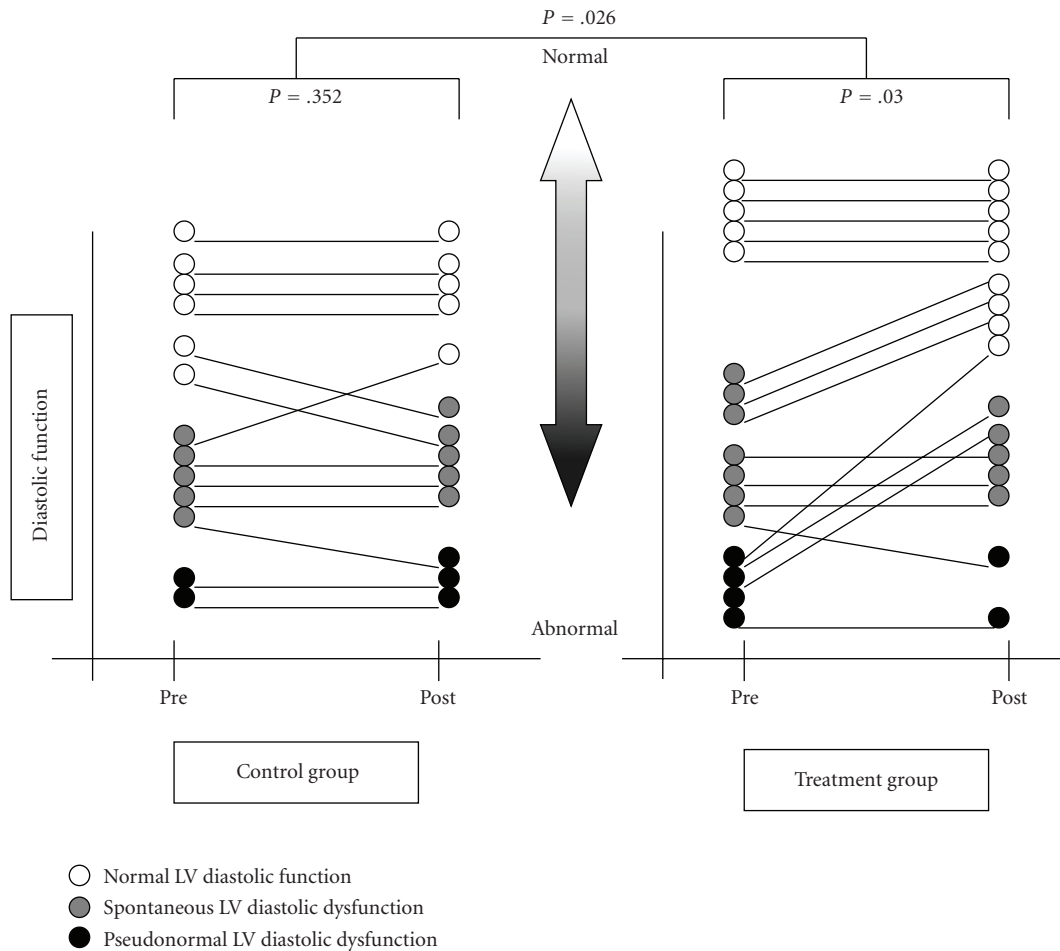
FIGURE 1: Changes in left ventricular (LV) diastolic function in both groups pre and posttreatment.

daytime. These associations suggest that improvement in the parasympathetic function is related to improvement in the cardiac LV diastolic function parameters, as we previously reported in overweight subjects with diabetes [21]. Of note, there are only few reported studies using pharmacological approach in severely obese patients [30–32] and HRV and diastolic function has not been evaluated within the same study in this population.

The magnitude of weight loss induced by the medication is smaller ($2.9 \pm 2.5\%$) but may be comparable to findings previously reported, accounting for the time-treatment period. Sjöström et al. have reported a 10% weight lost (10 kg) after a year of treatment with Orlistat in a cohort of overweight to severely obese subjects [33]. Other studies using Orlistat for a longer period (12 to 24 months) have also reported similar results [34–39]. Taking into account that our study only lasted three months, we may speculate that subjects of our study could have possibly lost comparable amount of weight if had our study lasted 12 months. Indubitably, the definitive treatment in this obesity category is bariatric surgery, but clinicians aim at a 5%–10% weight loss in order to achieve better metabolic profile in obese subjects [1, 15]. Fasting glycemia significantly decreased

in the treated group in contrast to the control group. Accordingly, Fujioka et al. [40] reported that every 4.5 kg reduction in weight should result in a 1.1 mmol/L decrement in fasting glycemia and to a 0.5% reduction in HbA_{1c}. Accordingly, HbA_{1c} values have significantly decreased in the treated group. However, we also observed a significant decrease in HbA_{1c} in the control group, which was not different to the decrease observed in the treated group. We also observed a significant decrease in LDL cholesterol in the treated group as well as in the control group. This is not unusual and it is often encountered in placebo groups of weight loss studies. Indeed, similar results have been reported in obese subjects after a 4-week run-in period before treatment with Orlistat [34, 35]. Studies [38, 39] in overweight to obese type 2 diabetic patients with longer treatment duration (6 to 12 months) resulting to greater weight loss report greater changes in metabolic profiles, leading after 12 months to significant differences between Orlistat-treated group and control group.

We acknowledge that this study included a small number of subjects. Therefore, it should be considered as a pilot study. However, weight loss was significant in the treated group whereas it was not in the control group. Also, a

few echocardiographic measurements, mainly those regarding the pulmonary veins assessment, were not adequately recorded because of technical reasons due to the corpulence of the subjects. Mitral inflow velocities are known to be load-dependent. Other indices of LV diastolic function, such as tissue Doppler-derived indices, may be less load-dependent. However, Dumesnil et al. [41] reported that tissue Doppler-derived indices are not totally preload independent and should be interpreted in light of the other Doppler parameters and the use of Valsalva's manoeuvre.

5. Summary

The aim of this study was to determine the impact of Orlistat-induced weight loss on the metabolic profile and cardiovascular function in severely obese type 2 diabetes patients. Twenty-nine severely obese patients with type 2 diabetes were randomized either to a nonplacebo control group or to a treatment group with Orlistat thrice a day. Metabolic profile, anthropometric parameters, heart rate variability indices, and echocardiographic variables were measured before and after a 12-week treatment period. Our results suggest that a modest weight loss improves fasting glycemia, diastolic function, and sympathovagal balance in severely obese patients with type 2 diabetes.

6. Conclusions

Despite modest but significant weight loss, we observed that subjects treated with Orlistat showed improvements in fasting glycemia. We also observed improvements in HRV as well as in the LV diastolic function. The improvement in the cardiac parasympathetic ANS modulation was associated with enhancement in LV diastolic function. Our results emphasize the benefit of even modest weight loss in severely obese patients with diabetes.

Disclosures

Acknowledgments

References

[1] P. Poirier, T. D. Giles, G. A. Bray et al., "Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 AmericanHeart Association Scientific Statement on obesity and heart disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism," *Circulation*, vol. 113, no. 6, pp. 898–918, 2006.

[2] H. R. Peterson, M. Rothschild, C. R. Weinberg, R. D. Fell, K. R. McLeish, and M. A. Pfeifer, "Body fat and the activity of the autonomic nervous sytem," *New England Journal of Medicine*, vol. 318, no. 17, pp. 1077–1083, 1988.

[3] J. Hirsch, R. L. Leibel, R. Mackintosh, and A. Aguirre, "Heart rate variability as a measure of autonomic function during weight change in humans," *American Journal of Physiology*, vol. 261, no. 6, part 2, pp. R1418–R1423, 1991.

[4] K. Karason, H. Mølgaard, J. Wikstrand, and L. Sjöström, "Heart rate variability in obesity and the effect of weight loss," *American Journal of Cardiology*, vol. 83, no. 8, pp. 1242–1247, 1999.

[5] E. Bobbioni-Harsch, J. Sztajzel, V. Barthassat et al., "The effect of insulin on cardiac autonomic balance predicts weight reduction after gastric bypass," *Diabetologia*, vol. 48, no. 7, pp. 1258–1263, 2005.

[6] Y. Akehi, H. Yoshimatsu, M. Kurokawa et al., "VLCD-induced weight loss improves heart rate variability in moderately obese Japanese," *Experimental Biology and Medicine*, vol. 226, no. 5, pp. 440–445, 2001.

[7] P. Poirier, T. L. Hernandez, K. M. Weil, T. J. Shepard, and R. H. Eckel, "Impact of diet-induced weight loss on the cardiac autonomic nervous system in severe obesity," *Obesity Research*, vol. 11, no. 9, pp. 1040–1047, 2003.

[8] M. Facchini, G. Malfatto, L. Sala et al., "Changes of autonomic cardiac profile after a 3-week integrated body weight reduction program in severely obese patients," *Journal of Endocrinological Investigation*, vol. 26, no. 2, pp. 138–142, 2003.

[9] P. Rissanen, A. Franssila-Kallunki, and A. Rissanen, "Cardiac parasympathetic activity is increased by weight loss in healthy obese women," *Obesity Research*, vol. 9, no. 10, pp. 637–643, 2001.

[10] M. A. Alpert, C. R. Lambert, H. Panayiotou et al., "Relation of duration of morbid obesity to left ventricular mass, systolic function, and diastolic filling, and effect of weight loss," *American Journal of Cardiology*, vol. 76, no. 16, pp. 1194–1197, 1995.

[11] L. Backman, U. Freyschuss, D. Hallberg, and A. Melcher, "Reversibility of cardiovascular changes in extreme obesity. Effects of weight reduction through jejunoileostomy," *Acta Medica Scandinavica*, vol. 205, no. 5, pp. 367–373, 1979.

[12] M. A. Alpert, C. R. Lambert, B. E. Terry et al., "Effect of weight loss on left ventricular mass in nonhypertensive morbidly obese patients," *American Journal of Cardiology*, vol. 73, no. 12, pp. 918–921, 1994.

[13] H. J. Willens, S. C. Chakko, P. Byers et al., "Effects of weight loss after gastric bypass on right and left ventricular function assessed by tissue doppler imaging," *American Journal of Cardiology*, vol. 95, no. 12, pp. 1521–1524, 2005.

[14] O. J. Rider, J. M. Francis, M. K. Ali et al., "Beneficial cardiovascular effects of bariatric surgical and dietary weight loss in obesity," *Journal of the American College of Cardiology*, vol. 54, no. 8, pp. 718–726, 2009.

[15] S. Klein, L. E. Burke, G. A. Bray et al., "Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism," *Circulation*, vol. 110, no. 18, pp. 2952–2967, 2004.

[16] "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report. National Institutes of Health," *Obesity Research*, vol. 6, supplement 2, pp. 51S–209S, 1998.

[17] N. Finer, W. P. T. James, P. G. Kopelman, M. E. J. Lean, and G. Williams, "One-year treatment of obesity: a randomized, double-blind, placebo-controlled, multicentre study of orlistat, a gastrointestinal lipase inhibitor," *International Journal of Obesity*, vol. 24, no. 3, pp. 306–313, 2000.

[18] M. T. La Rovere, G. D. Pinna, R. Maestri et al., "Short-term heart rate variability strongly predicts sudden cadiac death in chronic heart failure patients," *Circulation*, vol. 107, no. 4, pp. 565–570, 2003.

[19] M. M. Redfield, S. J. Jacobsen, J. C. Burnett, D. W. Mahoney, K. R. Bailey, and R. J. Rodeheffer, "Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic," *Journal of the American Medical Association*, vol. 289, no. 2, pp. 194–202, 2003.

[20] P. Poirier, P. Bogaty, C. Garneau, L. Marois, and J. G. Dumesnil, "Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy," *Diabetes Care*, vol. 24, no. 1, pp. 5–10, 2001.

[21] P. Poirier, P. Bogaty, F. Philippon, C. Garneau, C. Fortin, and J. G. Dumesnil, "Preclinical diabetic cardiomyopathy: relation of left ventricular diastolic dysfunction to cardiac autonomic neuropathy in men with uncomplicated well-controlled type 2 diabetes," *Metabolism*, vol. 52, no. 8, pp. 1056–1061, 2003.

[22] W. T. Friedewald, R. I. Levy, and D. S. Fredrickson, "Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge," *Clinical Chemistry*, vol. 18, no. 6, pp. 499–502, 1972.

[23] "Guidelines from the Canadian Cardiovascular Society and the Canadian Hypertension Society on the echocardiographic determination of left ventricular mass. Task Force of the Echocardiography Section," *The Canadian Journal of Cardiology*, vol. 11, no. 5, pp. 391–395, 1995.

[24] D. Levy, D. D. Savage, and R. J. Garrison, "Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study," *American Journal of Cardiology*, vol. 59, no. 9, pp. 956–960, 1987.

[25] "Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," *European Heart Journal*, vol. 17, no. 3, pp. 354–381, 1996.

[26] R. R. Jhaveri, K. K. Pond, T. H. Hauser et al., "Cardiac remodeling after substantial weight loss: a prospective cardiac magnetic resonance study after bariatric surgery," *Surgery for Obesity and Related Diseases*, vol. 5, no. 6, pp. 648–652, 2009.

[27] S. Chakko, M. Mayor, M. D. Allison, K. M. Kessler, B. J. Materson, and R. J. Myerburg, "Abnormal left ventricular diastolic filling in eccentric left ventricular hypertrophy of obesity," *American Journal of Cardiology*, vol. 68, no. 1, pp. 95–98, 1991.

[28] E. Kanoupakis, D. Michaloudis, O. Fraidakis, F. Parthenakis, P. Vardas, and J. Melissas, "Left ventricular function and cardiopulmonary performance following surgical treatment of morbid obesity," *Obesity Surgery*, vol. 11, no. 5, pp. 552–558, 2001.

[29] A. Alaud-din, S. Meterissian, R. Lisbona, L. D. MacLean, and R. A. Forse, "Assessment of cardiac function in patients who were morbidly obese," *Surgery*, vol. 108, no. 4, pp. 809–818, 1990.

[30] D. H. Ryan, W. D. Johnson, V. H. Myers et al., "Nonsurgical weight loss for extreme obesity in primary care settings: results of the Louisiana Obese Subjects Study," *Archives of Internal Medicine*, vol. 170, no. 2, pp. 146–154, 2010.

[31] J. J. G. Martínez, F. A. Ruiz, and S. D. Candil, "Baseline serum folate level may be a predictive factor of weight loss in a morbid-obesity-management programme," *British Journal of Nutrition*, vol. 96, no. 5, pp. 956–964, 2006.

[32] G. De Simone, C. Romano, C. De Caprio et al., "Effects of sibutramine-induced weight loss on cardiovascular system in obese subjects," *Nutrition, Metabolism and Cardiovascular Diseases*, vol. 15, no. 1, pp. 24–30, 2005.

[33] L. Sjöström, A. Rissanen, T. Andersen et al., "Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients," *Lancet*, vol. 352, no. 9123, pp. 167–172, 1998.

[34] J. Hauptman, C. Lucas, M. N. Boldrin, H. Collins, and K. R. Segal, "Orlistat in the long-term treatment of obesity in primary care settings," *Archives of Family Medicine*, vol. 9, no. 2, pp. 160–167, 2000.

[35] M. H. Davidson, J. Hauptman, M. DiGirolamo et al., "Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial," *Journal of the American Medical Association*, vol. 281, no. 3, pp. 235–242, 1999.

[36] F. Lindgarde, "The effect of orlistat body weight and coronary heart disease risk profile in obese patients: the swedish multimorbidity study," *Journal of Internal Medicine*, vol. 248, no. 3, pp. 245–254, 2000.

[37] J. H. Zavoral, "Treatment with orlistat reduces cardiovascular risk in obese patients," *Journal of Hypertension*, vol. 16, no. 12, part 2, pp. 2013–2017, 1998.

[38] P. A. Hollander, S. C. Elbein, I. B. Hirsch et al., "Role of orlistat in the treatment of obese patients with type 2 diabetes: a 1-year randomized double-blind study," *Diabetes Care*, vol. 21, no. 8, pp. 1288–1294, 1998.

[39] D. E. Kelley, L. H. Kuller, T. M. McKolanis, P. Harper, J. Mancino, and S. Kalhan, "Effects of moderate weight loss and orlistat on insulin resistance, regional adiposity, and fatty acids in type 2 diabetes," *Diabetes Care*, vol. 27, no. 1, pp. 33–40, 2004.

[40] K. Fujioka, T. B. Seaton, E. Rowe et al., "Weight loss with sibutramine improves glycaemic control and other metabolic parameters in obese patients with type 2 diabetes mellitus," *Diabetes, Obesity and Metabolism*, vol. 2, no. 3, pp. 175–187, 2000.

[41] J. G. Dumesnil, C. Paulin, P. Pibarot, D. Coulombe, and M. Arsenault, "Mitral annulus velocities by Doppler tissue imaging: practical implications with regard to preload alterations, sample position, and normal values," *Journal of the American Society of Echocardiography*, vol. 15, no. 10, part 2, pp. 1226–1231, 2002.