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Randomized Control Trials

Effect of a chronotype-adjusted diet on weight loss effectiveness: A randomized clinical trial

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SUMMARY

Background & aims: The alteration of normal biological rhythms, also known as chronodisruption, may be associated with obesity development. For instance, those subject with preference for vespertinity seem to be prone to develop obesity. However, the current hypocaloric dietary treatment of obesity does not take into account these aspects. Therefore, the objective of this trial was to evaluate whether a diet adjusted to patient's chronotype is more effective than the current dietary recommendations.

Methods: 209 subjects take part on a 3 month randomized, double-blind trial. 104 subjects followed a typical hypocaloric dietary treatment and the other 105 subjects undergone a diet with a daily caloric distribution adjusted to their chronotype. There were no sex or age differences between groups.

Results: Baseline characteristics were similar in both groups. Dropout rate was also similar in both interventions ($p = 0.683$). Although both groups improved their anthropometrical parameters, the chronotype-adjusted diet group achieved a statistically significant greater reduction in percentage of total body weight loss (%TWL), BMI and waist circumference than the control group ($p < 0.010$ in all contrasts). The effect on clinical parameters was less pronounced.

Conclusions: This randomized trial has demonstrated for the first time that in overweight/obese subjects, a chronotype-adjusted diet is more effective than the traditional hypocaloric dietary treatment, at least regarding the anthropometrical parameters. Further research will confirm if this intervention is also more effective in the long term.

Trial registration: NCT-ID: #NCT03755674, (available at: <http://www.clinicaltrials.gov>).

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1. Introduction

Obesity is a condition with evident deleterious effects on human health. Unfortunately, obesity prevalence has increased dramatically for the last 30 years, and its prevalence in several countries like UK or USA will reach 60% in 2020–2030 [1]. Although obesity has been classically associated to an excess of calorie intake, in the last decades, the amount of calories ingested not only has not increased, but also it has decreased; however, the prevalence of obesity has continued to increase alarmingly [2].

It is unlikely that the increase of obesity prevalence might be explained only on basis on genetic modifications, since it is a too small period to allow such changes, therefore, several theories have been proposed to explain this apparent paradox, and environmental (epigenetics) [3], psychological [4] and social [5] factors have been proposed as possible determinants of obesity development.

Whatever the responsible factor, patients with obesity are not able to balance their energy intake with their caloric expenditure [6]. Thus, the study of the mechanisms involved in body weight regulation in human is essential to adequately address this pathology. In this regard, numerous evidences have demonstrated the influence of circadian rhythms (chronotype) in the development of overweight and obesity [7]. Erren et al. first established the term chronodisruption as a desynchronization of the 24-h rhythms in a

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chronic manner, resulting in adverse health effects [8]. This may occur when synchronization between the environmental cues and physiological processes are lost, and can induce several alterations in phase rhythmicity between central nervous system and peripheral clocks, modifying subject's metabolism [6].

Previous reports have demonstrated a relationship between the patient's chronotype (related to the patient time of ingestion) and eating habits, as well as the importance of adjusting these habits to the physiological rhythms of the patients [9,10]. Thus, an alteration of the eating patterns regulated by the circadian rhythms may also play a key role in obesity development [11]. Similarly, adjusting the caloric intake timing with the circadian clock system of the patient may be a useful tool to obesity treatment.

Although there are numerous clinical and experimental studies demonstrating the relation between the food timing and the risk of developing obesity [11,12], to the best of our knowledge, no previous study has been carried out in order to analyse the effectiveness of a hypocaloric dietary treatment adjusted to the patient's chronotype for the treatment of obesity. In fact, present obesity treatment is carried out following the general recommendations for the whole population, irrespective of the patient's chronotype. Therefore, the objective of the present study was to analyse the effect of a hypocaloric diet adjusted to the chronotype of the patient versus a diet with a conventional caloric distribution on weight loss.

2. Subject and methods

2.1. Study overview

A 12-week randomized plus one year follow-up, double-blind, parallel group controlled trial was conducted between September 2016 and December 2017 in the Catholic University of Murcia. The protocol of this randomized trial adheres to the CONSORT guidelines [13].

A researcher (J.J.H.M.) carried out the randomization, with the assistance of a macro designed in Visual Basic for the Microsoft Excel program. Randomization divided the participants in two groups, depending on whether they were treated with a hypocaloric diet (CONTROL group), or the group that followed a chronotype-adjusted diet (CHRONO group). In order to obtain a similar size in both groups, a randomization in blocks with a 1:1 allocation ratio was performed. Supporting CONSORT checklist for this trial and is available as [Supplementary material 1](#).

To study the influence of a chronotype-adjusted diet on weight loss, a double blind (de facto masking) trial was designed: both participants and the researchers who carried out the dietary treatment did not know the purpose of the study. Participants were unconscious of treatments and possible assignments between groups. The study was carried out after receiving written authorization from the Ethics Committee of the Catholic University of Murcia. Participants were informed, either orally or in writing, about the study design. They were also given an explanation of the ethical aspects of the project, informing the patients about the main objective of the study and guaranteeing the confidentiality and anonymity of the data, in accordance with the Declaration of Helsinki and Biomedical Research Spanish Law. All participants provided written informed consent.

2.2. Participants

In this project, 209 overweight/obese subjects (subjects with BMI > 25 kg/m²) were selected. The target population consisted of subjects who were overweight or obese and aged between 18 and 65 years. The selection was made through e-mail and

advertisements. Those subjects with significant cognitive impairment, psychiatric disorders or chronic pharmacological treatment that may affect the effectiveness of the dietary intervention (corticosteroids, thyroid hormones, oral antidiabetic agents or lipid-lowering drugs) were excluded. A chronic disease that may interfere with dietary therapy (cancer, renal or hepatic impairment, chronic gastrointestinal conditions), or acute disease episodes during the study were also established as exclusion criteria. Those subjects who had followed a hypocaloric diet at the allocation time or in the 3 months prior to the beginning of the study were also excluded.

The sample was randomly divided in two groups of 104 and 105 subjects each, in which one group was treated with a hypocaloric diet adjusted to the chronotype (morning/evening) (CHRONO group) and the other with a standard balanced diet (CONTROL group). The Horne-Östberg questionnaire was used to evaluate morning and evening chronotypes [14]. According to the scores obtained, the subjects of the CHRONO group were classified into two categories, low scorers (16–51 points), which was associated with the evening, and high scorers (52–86 points) that were associated with the morning chronotype.

2.3. Intervention

Overweight/obese patients followed a 3-month (12 weeks) hypocaloric dietary treatment. Hypocaloric diets were designed following the SEEDO and FESNAD (Spanish Federation of Nutrition, Food and Dietetics) guidelines [15]. Patients were instructed to modify their usual diet by a balanced diet following a nutrient distribution based on the Mediterranean Diet. These diets were designed to provide patients with the following nutrient distribution: 50–60% carbohydrates, 30–35% fats and 15–20% proteins. Patients were monitored weekly to record their changes in body weight and body composition for 12 weeks. A dietitian (JSGM) designed diets with the assistance of Dietowin 8.0 software (BI-Biologica, Barcelona, Spain). This program includes the nutritional composition of more than 600 foods, according to the tables of Spanish food composition. Program food database was modified to be adapted to some foods of frequent consumption, as well as to some typical recipes of the Region of Murcia. In addition, participants were suggested to carry out 30 min of moderate aerobic exercise for at least 5 days per week (150 min/week), as recommended [15].

Although the daily energy intake and nutrient distribution were similar in both groups, the dietary treatment varied according to the intervention group. Specifically, hypocaloric diets in the CONTROL group were structured in five meals, attending to the following daily total energy intake distribution: breakfast 20%, mid-morning 10%, lunch 35%; mid-afternoon 10% and dinner 25%. On the other hand, the caloric distribution for the morning subjects included in the CHRONO group was as follow: breakfast 30%, mid-morning 10%, lunch 35%; mid-afternoon 5% and dinner 20% for morning subjects, whereas for evening subjects, the caloric distribution was: breakfast 20%, mid-morning 5%, lunch 35%; mid-afternoon 10% and dinner 30%. The maximum variability allowed in every meal was $\pm 1\%$. Diets were designed according to patients' preferences, and unwanted meals were excluded from the menus. Total caloric intake was estimated through the subject's basal metabolic rate and physical activity level, again according to SEEDO-FESNAD procedures [15]. Hypocaloric diets were designed based on a reduction of 1000 kcal/day, trying to get a weight loss of 0.5–1 kg/week. Approximately, the daily energy estimation of the hypocaloric diets was of 1600–2000 kcal/d for men and 1000–1500 kcal/d for women. The total energy expenditure was recalculated weekly, and the total energy expenditure of the

hypocaloric diets was reformulated in the same base to try to accurately adjust to the energy requirements of the patient.

2.4. Outcomes measures

The primary efficacy end-point was change in total weight loss percentage (%TWL) from baseline to week 12, as recommended by the SEEDO and NAASO associations. Key secondary efficacy end-points included changes from baseline to 12th week in anthropometrical (BMI, body fat and waist circumference) and biochemical parameters. A one year follow-up of the anthropometrical parameters was also planned to study the long-term effect of the intervention.

2.5. Anthropometrical data

Anthropometric variables were evaluated according to the criteria proposed by the SEEDO in 2007 [16]. The parameters of weight, percentage of fat mass and fat free mass were measured by bioelectrical impedance analysis, with a TANITA BC-418® (TANITA Corporation of America, Inc., Arlington Heights, IL, USA). The height was measured with a TANITA rod (model Harpender), with the subject barefoot, erect and with the head aligned according to the Frankfurt plane. The BMI was calculated using these data. The distribution of body fat was analysed with the measurement of waist circumference. Each measurement was performed 3 times, in a non-consecutive way, by the same investigator.

2.6. Metabolic syndrome parameters and clinical determinations

After an intravenous blood sample extraction at the beginning and at the end of the study, the biochemical parameters of cHDL, TG and basal glucose were analysed with the Reflotron® Plus (Roche Diagnostics, Switzerland), using Reflotron reagents. TG and basal glucose were analysed from total venous blood samples, whereas cHDL was determined from plasma samples, following the manufacturer indications. All biochemical parameters were measured in the fasted state. In addition, the Atherogenicity Index (TG/cHDL) and the presence of metabolic syndrome (SMet) were determined [17].

2.7. Statistical analysis

The necessary sample size was determined using the program GPower 3.0 [18]. The sample size was calculated according to our previous report [19], taking into account a confidence level ($1 - \alpha$) of 95% and considering a power (β) of 80%; we selected a difference of effect between groups or effect size (d) equal to 10 kg. The standard deviation (σ) selected was 10 kg, taking into account our previous study [19], resulting in 42 subjects per group. Considering an estimated drop-out rate of 50% (treatment withdrawal) (also based on the previous study), the final minimum sample for the present study was 84 subjects per group. Figure 1 shows the flow diagram followed for the patients' recruitment and selection procedures.

First, a basic statistical descriptive study to analyse the general characteristics of the population studied was performed on the data obtained from the full analysis set, including all randomized subjects. The analysis of primary and secondary end-points was conducted on a modified intention-to-treat population, following a pre-specified imputation method, which was the last-observation carried forward. This imputation included all randomized subjects whom undergone at least one week of treatment, so that at least two measurements are available (baseline and week 1). The consistency of the primary analysis was studied by multiple

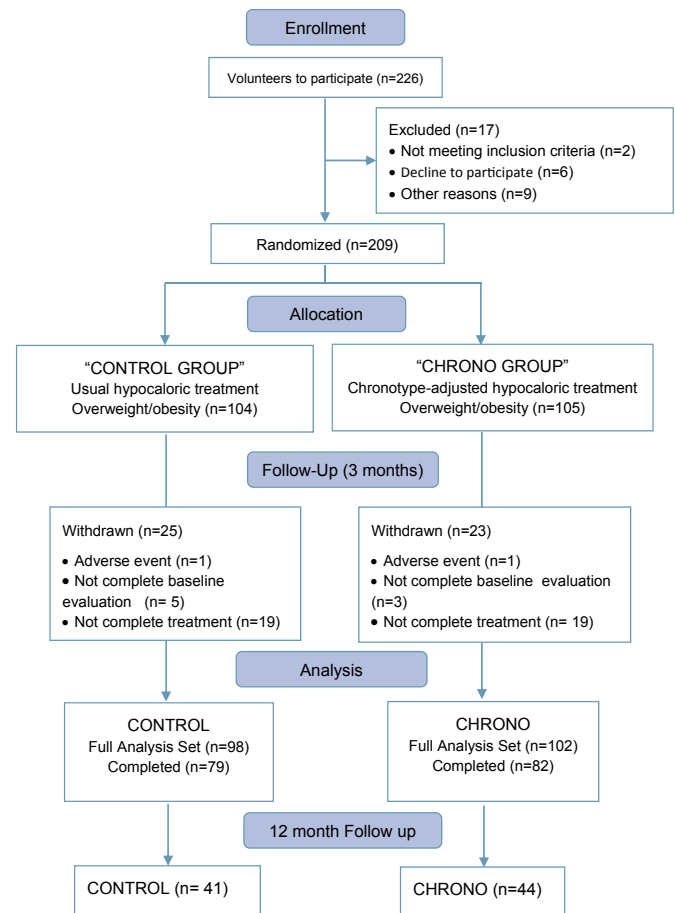


Fig. 1. Flow diagram of the trial.

sensitivity analyses (Supplementary material 2), using several methods for handling missing data, as suggested by the ICH guidelines [20] and CONSORT guidelines [13].

Baseline characteristic differences were analysed by a *t*-test. In order to analyse the changes in anthropometrical parameters during the treatment, a pre-specified ANCOVA test was performed, with two factors, weekly weight loss considered as within-subject, and group (CONTROL vs CHRONO) as between-subjects. In this procedure, sex, age and baseline anthropometrical values were considered as covariates, and treatment as fixed effect.

All statistical tests were performed considering a level of significance equal to $p < 0.050$. The analysis was performed using SPSS statistical software (version 22.0.7, SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Trial population baseline characteristics

Table 1 shows the general baseline characteristics of the study population. Considering that the allocation of the subjects was completely randomized, we did not observe any statistically significant difference regarding the baseline characteristics of the population studied, as would be expected.

At the end of the intervention, the dropout rate was of 22% in those patients undergoing a caloric distribution adjusted to the chronotype (CHRONO group). In the control group, the dropout rate was slightly higher (24%), however, no significant relationship was observed between the treatment and the dropout rate ($\chi^2 = 0.167$,

Table 1
Clinical baseline characteristics of the population studied.

	CONTROL (n = 98)	CHRONO (n = 102)	p
Age (y)	44.8 ± 9.7	45.1 ± 9.1	0.903
Weight (kg)	83.0 ± 9.6	83.3 ± 9.6	0.805
BMI (kg/m ²)	31.00 ± 3.2	30.73 ± 2.56	0.330
Waist (cm)	99.8 ± 7.9	100.6 ± 7.4	0.257
Body fat (%)	37.0 ± 9.2	36.6 ± 8.5	0.656
Fat free mass (kg)	51.8 ± 5.7	52.7 ± 6.8	0.141
SBP (mmHg)	130 ± 12	128 ± 17	0.732
DBP (mmHg)	79 ± 9	77 ± 9	0.334
Fasting glucose (mg/dl)	101.1 ± 27.7	104.7 ± 33.0	0.390
Triglycerides (mg/dl)	164.6 ± 85.8	150.5 ± 122.5	0.855
cHDL (mg/dl)	45.6 ± 19.6	42.5 ± 19.1	0.405
Atherogenicity Index	4.2 ± 1.1	5.1 ± 1.8	0.223

Mean ± SD. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; cHDL: high-density level cholesterol; Atherogenicity index estimated as triglycerides/cHDL. Statistical differences were analysed in the full-set population, and were estimated by mean of a Student's *t* test. Statistical significance level was set at $p < 0.050$.

$p = 0.683$). At 12 months, the loss of follow-up was also similar in both groups.

3.2. Body weight and anthropometric parameter end points

The effect of the different interventions on the anthropometric parameters is shown in Fig. 2. Although both groups improved their anthropometrical parameters, the chronotype-adjusted diet group achieved a statistically significant greater reduction in percentage of total body weight loss (%TWL), BMI, and waist circumference than the control group, undergoing a usual hypocaloric treatment.

These differences still remain significant for the primary outcome in the different statistical procedures described in the sensitivity analysis (Supplementary material 2). The Fat Free Mass decrease was slightly but significantly higher in the chrono group, probably as a consequence of a higher body weight loss.

To study the evolution of anthropometric parameters over the twelve weeks of treatment, a repeated measures ANCOVA analysis using the clinical variable of interest as within-subject factor and the type of treatment as between-subject factor was performed. Figure 3 shows a progressive decrease in %TWL in both treatment groups ($p < 0.001$). In addition, the analysis revealed a significant interaction effect between both factors (weight loss × treatment type, $p = 0.018$). Similarly, when the variation in BMI over the 12 weeks of treatment was analysed, our data indicated a significant reduction in both groups ($p < 0.001$), although in this case, the interaction was not statistically significant ($p < 0.079$) (Fig. 3b). The results obtained regarding waist circumference and body fat showed a similar trend (Fig. 3c and d respectively).

Taking into account that the CHRONO group was composed of both morning and evening subjects, we further analysed if there were statistical differences in treatment efficacy between both chronotypes (Supplementary material 3). However, our data showed no statistical differences regarding the improvement of anthropometric parameters depending on the patients' chronotype.

When anthropometrical parameters were re-evaluated after one year of follow-up, the data still indicated a greater effect of the treatment in the chrono group, although the estimated treatment differences and the statistical significance were lower than in the first evaluation (Fig. 2).

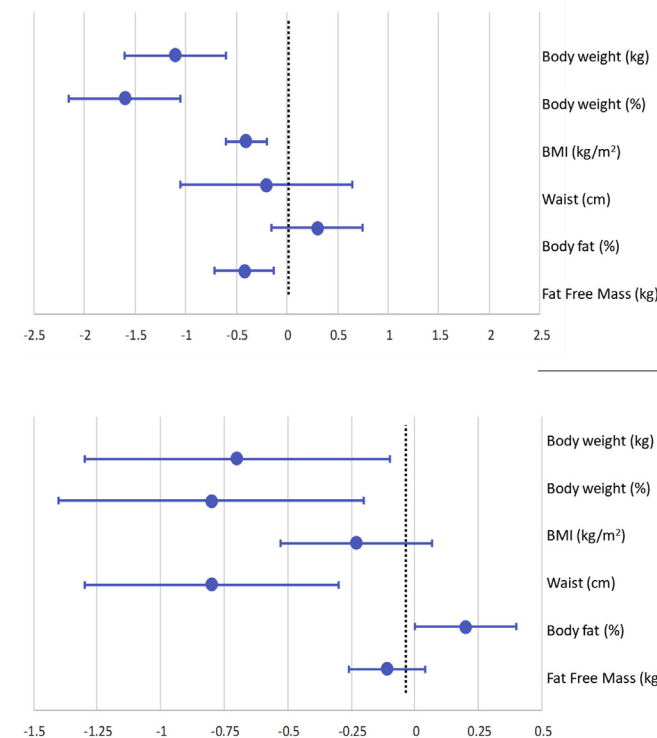


Fig. 2. Changes in anthropometric parameters end points after 12 weeks of treatment (upper) and after 12 months of follow-up (lower). Estimated treatment differences (odds ratio and 95% CIs) are shown in the Forest plots. Baseline anthropometrical parameters are shown as mean ± SD. Data are derived from those patients with at least one post-baseline assessment. Those participants without any post-baseline assessment were excluded from the analyses; BMI: body mass index. Body weight (%) refers to changes in the percentage of body weight, or percentage of total body weight loss.

	BASELINE		Observed mean ± sd change from baseline at week 12		Estimated treatment difference (95% CI)	p-value
	Control (n=48)	CHRONO (n=48)	Control (n=48)	CHRONO (n=48)		
Body weight (kg)	83.0 ± 9.6	83.3 ± 9.6	-7.2 ± 0.2	-8.2 ± 0.2	-1.0 (-1.4 to -0.6)	<0.001
Body weight (%)	-	-	-8.5 ± 2.5	-9.9 ± 2.1	-1.4 (-1.8 to -1.0)	<0.001
BMI (kg/m ²)	31.00 ± 3.2	30.73 ± 2.56	-2.65 ± 0.94	-3.04 ± 0.88	-0.40 (-0.57 to -0.24)	<0.001
Waist (cm)	99.8 ± 7.9	100.6 ± 7.4	-8.1 ± 3.6	-9.2 ± 2.6	-1.0 (-1.7 to -0.3)	0.001
Body fat (%)	37.0 ± 9.2	36.6 ± 8.5	-4.0 ± 1.4	-3.9 ± 2.0	0.1 (-0.2 to 0.4)	0.570
Fat Free Mass (kg)	51.8 ± 5.7	52.7 ± 6.8	-1.6 ± 1.5	-2.0 ± 1.8	-0.42 (-0.71 - 0.13)	0.005

	Control (n=98)	CHRONO (n=102)	Control (n=41)	CHRONO (n=44)		
Body weight (kg)	83.0 ± 9.6	83.3 ± 9.6	-5.6 ± 3.1	-6.3 ± 2.4	-0.7 (-1.3 to -0.2)	0.007
Body weight (%)	-	-	-6.5 ± 3.5	-7.3 ± 2.7	-0.8 (-1.4 to -0.2)	0.007
BMI (kg/m ²)	31.00 ± 3.2	30.73 ± 2.56	-1.88 ± 1.48	-2.11 ± 1.43	-0.23 (-0.51 to 0.05)	0.112
Waist (cm)	99.8 ± 7.9	100.6 ± 7.4	-4.2 ± 2.7	-5.0 ± 3.0	-0.8 (-1.3 to -0.2)	0.007
Body fat (%)	37.0 ± 9.2	36.6 ± 8.5	-3.2 ± 2.3	-3.0 ± 0.8	0.2 (-0.2 to 0.6)	0.394
Fat Free Mass (kg)	51.8 ± 5.7	52.7 ± 6.8	-0.6 ± 1.1	-0.7 ± 1.2	-0.11 (-0.26 - 0.04)	0.464

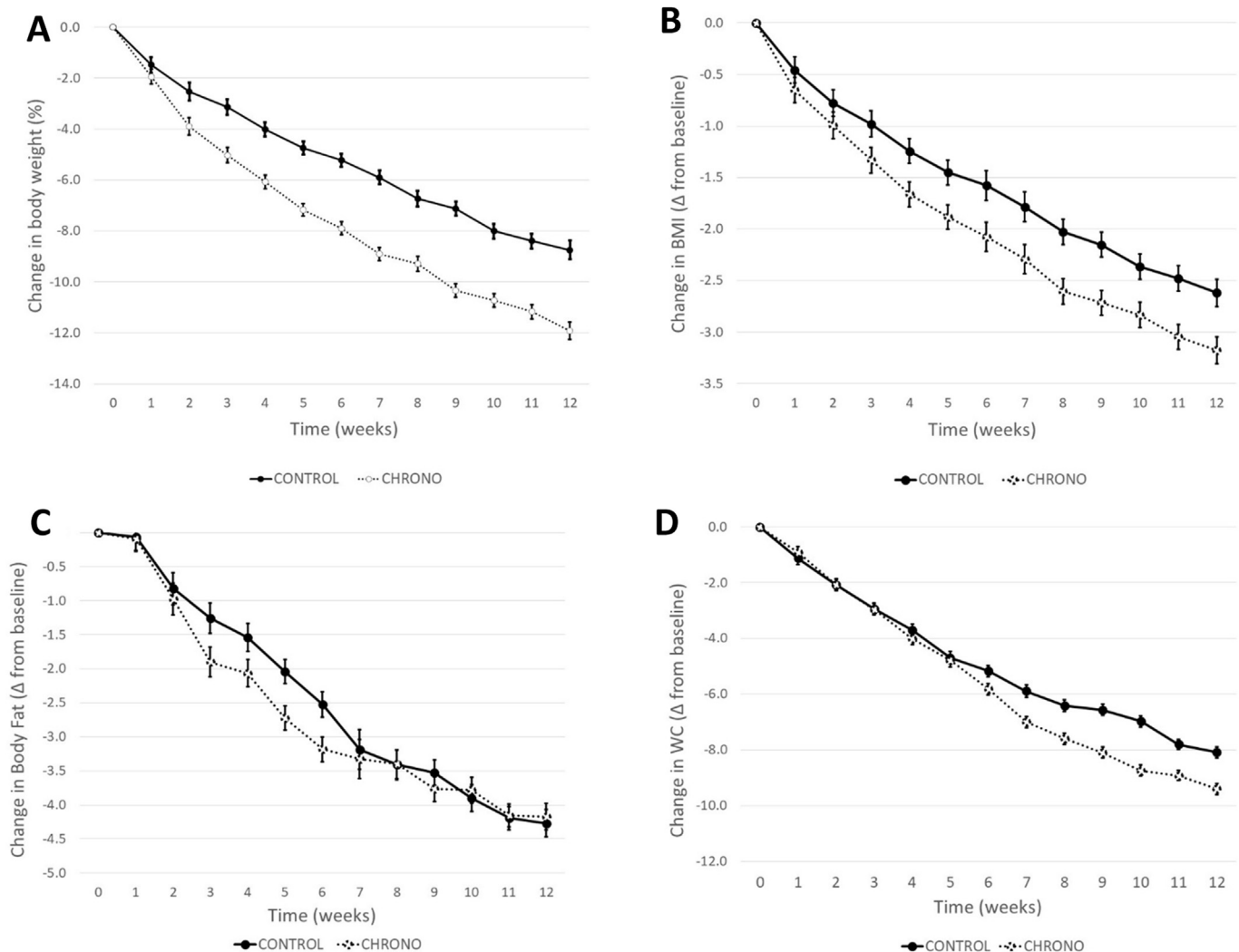


Fig. 3. Change in anthropometrical parameters over 12 weeks of treatment. (A) Changes in percentage of total weight loss, (B) Changes in BMI, (C) Changes in body fat percentage and (D) Changes in waist circumference. Data are derived from the full analysis set (Last observation carried forward). Those participants without any post-baseline assessment were excluded from the analyses. Data are mean $\pm$ SE.

3.3. Clinical and biochemical parameter end points

As secondary end points of this clinical trial, the effect of a chronotype-adjusted diet on clinical parameters was also analysed, as shown in Fig. 4. After 12 weeks, both groups exhibited a significant improvement in all biochemical parameters. However, when comparing the effectiveness of both treatments, our data showed a significant higher effect on the chrono group regarding fasting plasma glucose and atherogenicity index, while the control group showed a higher decrease of plasma triglycerides, despite a great data variability.

A similar situation was observed regarding Metabolic Syndrome prevalence. In the present study, there was a significant reduction in the number of subjects diagnosed with MetS in both treatments (Supplementary material 4). Therefore, from the data obtained, it is not able to affirm treatment effect differences in reference to the clinical parameters.

4. Discussion

There are several evidences that have revealed the influence of circadian preferences or rhythms on overweight and obesity

development [7]. In a previous study, we already demonstrated the interaction between patient's chronotype and dietary habits, both in relation to the time of food ingestion and the kind of food ingested [9]. Several authors have highlighted the influence in overweight and obesity development of the time in which energy is eaten [10]. In general, these previous studies seem to confirm a protective role of higher energy and nutrient intake during the morning, which means that eating a breakfast rich in energy and nutrients may confer a protection against obesity [21]. Moreover, other studies have observed that, in obese patients undergoing a hypocaloric treatment, those who consumed the greatest amount of energy and nutrients during the morning reached the highest weight loss. The meal timing or more specifically, the macronutrient timing may have more relevance. As suggested by Sofer et al., a protein-rich breakfast and carbohydrates-rich dinner could be an interesting way to induce weight loss [22].

However, the variability of the results obtained in these previous reports was huge, probably because the interventions for a higher intake in the morning were made without taking into account the chronotype of the patients, and as previously commented, dietary habits are determined in part by the chronotype. For these reasons, in the present study we hypothesized that a diet

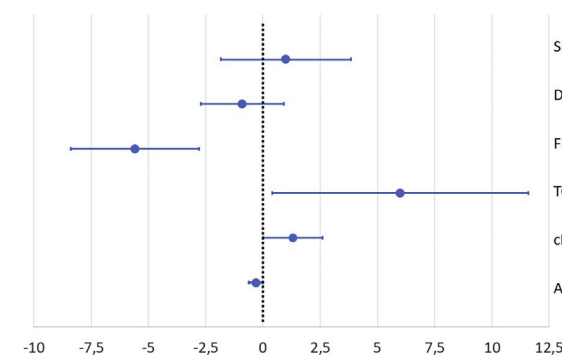


Fig. 4. Changes in clinical and biochemical parameters end points after 12 weeks of treatment. Estimated treatment differences (Odd Ratio and 95% CIs) are shown in the Forest plots. Baseline clinical parameters are shown as mean $\pm$ SD. Data are derived from those patients with at least one post-baseline assessment. Those participants without any post-baseline assessment were excluded from the analyses; SBP: systolic blood pressure; DBP: diastolic blood pressure; cHDL: high-density level cholesterol; Atherogenicity index estimated as triglycerides/cHDL.

with a caloric distribution adjusted to the patient's chronotype may be more effective than a simple hypocaloric diet with the traditional or recommended caloric distribution.

Considering that the ideal treatment for an obese patient is aimed to reach the greatest loss of body fat with the greatest maintenance of muscle mass, attending to the data obtained, our results confirmed that, regarding anthropometrical parameters, a chronotype-adjusted diet was more effective than a conventional hypocaloric diet for the treatment of overweight or obesity, since the percentage of total weight loss and the decrease on BMI was significantly higher in the chronotype-adjusted group (Chrono). Unfortunately, the decrease in fat free mass was also higher in the Chrono group, which could predispose these subjects to greater weight gain; however, the fat free mass loss observed in the present study was much lower than those described in other studies were ketogenic or unbalanced diets were employed [23,24], which emphasizes the suitability of this intervention.

A result to take into consideration is that both treatments achieved a regular weight loss on a weekly basis, although the Chrono group showed a higher efficacy especially during the first six weeks of treatment. Considering that both treatments were isocaloric, this result may indicate that at the beginning of the treatment, a chronotype-adjusted diet induces a higher energy expenditure, probably because the caloric intake is synchronized with the circadian metabolism regulated by the chronotype of the patients. From the sixth week, the effect was mainly similar in both groups, which could be indicating that the weight loss produced in the control group in these weeks readjusts or align the metabolism to the patient's circadian rhythm, something that might be expected since after the light cues, the strongest regulatory signals to engage circadian rhythm are the food cues.

Apparently, subjects with an evening chronotype have a worse eating pattern than morning subjects [25]. Arora and Taheri have observed a higher caloric intake and an inadequate intake of fruit and vegetables in evening subjects [26], whereas Kanerva et al. have described a higher consumption of sugary drinks [27]. However, our data indicated that weight reduction was similar in both morning and evening subjects, being always higher than in the control group. Considering that in both groups, the present dietary treatments were based on healthy habits, with a high consumption of fruits and vegetables, it is logical to assume that the evening

subjects have improved their eating pattern in the same way as morning subjects.

The effectiveness of a chronotype-adjusted diet in terms of biochemical parameters was not as evident as with the anthropometrical parameters. In this regard, both groups showed a clear improvement of fasting glucose, triglycerides and cHDL, probably due to the composition of the diet, being in both groups a Mediterranean diet. This diet is characterized by the high consumption of monounsaturated fatty acids, unrefined cereals, fruits, vegetables, nuts, moderate consumption of fish, and low consumption of red meat [28], all these factors being related to an improvement of the clinical parameters. This issue may indicate that, at least regarding biochemical parameters, nutrient or food composition is more relevant than the weight loss itself.

It is beyond the scope of the present study to delve into the benefits of the Mediterranean diet, and large population clinical trials have undoubtedly shown the advantages of this diet especially on cardiovascular risk factors, like the PREDIMED or the Lyon Diet Heart Study [29–32]. Nevertheless, in our opinion and attending to the data obtained, besides consuming food according to the Mediterranean diet recommendations, it is important to consume those foods according to our biological rhythms, since they will induce a better or worse use of the energy and nutrients contained in such foods.

At this point, several limitations of the study should be commented. On the one hand, the duration of the treatment was only 3 months, so it may be necessary a longer period to observe changes induced by the diet, especially regarding the biochemical parameters. There is a great controversy on this respect, since certain studies have described that 3 months of intervention are enough to observe significant improvement on these parameters; however, other studies have suggested the need for longer periods (up to 5 years) [27,31]. On the other hand, it would have been interesting a greater metabolic characterization of these patients, as for example by analysing the respiratory quotient, in order to be able to confirm if the nutrient metabolism (or catabolism in this case) was really higher in the Chrono group. Unfortunately, we did not obtain any bibliographical reference when using the terms "respiratory quotient + chronotype", so further researches will shed some light in this regard. On the other hand, the determination of other parameters that can be easily measured, like plasma insulin and the

calculation of the HOMA index, will help to check if there is or not a positive effect of a chronotype-adjusted diet on these parameters, and consequently, in the metabolism of these subjects. Finally, it should be commented that the effectiveness of the intervention was lower at long-term. This data was not unexpected since many reports have showed that hypocaloric diets alone are unsuccessful regarding long-term weight loss [33–35]; therefore, a multidimensional approach including behavioural therapies and, especially, physical activity interventions might be necessary in these patients to maintain weight loss at long-term [36,37].

In conclusion, this randomized clinical trial have demonstrated for the first time that in overweight/obese subjects, a chronotype-adjusted diet is more effective than the usual hypocaloric dietary treatment, at least regarding the anthropometrical parameters (% of total weight loss and BMI). Although undoubtedly new research is needed to know the precise physiological and metabolic mechanisms by which a chronotype-adjusted diet induces greater weight loss, at the moment, it might be of great interest to consider not only the patients' daily energy expenditure, but also their circadian preferences, in order to increase the effectiveness of hypocaloric diets.

Conflicts of interest

None of the authors have any competing interest to declare.

Authors' contributions

Conceptualization: J.J.H.M.; Data curation: C.M.M.C., M.C.B.O. Formal analysis: C.M.M.C.; Investigation: J.S.G.M., I.D.S. Methodology: J.J.H.M. Supervision: J.J.H.M. Visualization: C.M.M.C., M.C.B.O. Writing – review & editing: J.J.H.M., C.M.M.C., J.S.G.M. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnu.2019.05.012>.

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