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Comparative effects of glucagon-like peptide-1 receptors agonists, 4-dipeptidyl peptidase inhibitors, and metformin on metabolic syndrome☆

Cristina Bouzas [a,b,c], Rosario Pastor [b,d], Silvia Garcia [a,b,c], Margalida Monserrat-Mesquida [a,b,c], Miguel Ángel Martínez-González [a,e,f], Jordi Salas-Salvadó [a,g,h], Dolores Corella [a,i], Albert Goday [a,j], J. Alfredo Martínez [a,k,l], Ángel M. Alonso-Gómez [a,m], Olga Fernández-Barceló [n], Jesús Vioque [o,p], Dora Romaguera [a,c], José Lopez-Miranda [a,q], Ramón Estruch [a,r], Francisco J. Tinahones [a,s], José Lapetra [a,t], Lluís Serra-Majem [a,u], Blanca Riquelme-Gallego [p,v], Vicente Martín-Sánchez [p,w], Xavier Pintó [a,x], Miguel Delgado-Rodriguez [p,y], Pilar Matía [z], Josep Vidal [aa], Jersy-Jair Cardenas-Salas [ab], Lidia Daimiel [ac], Emilio Ros [a,ad], Estefanía Toledo [a,e], Josep M. Manzanares [g,h], Inmaculada Gonzalez-Monge [i], Miguel-Ángel Muñoz [a,j], Diego Martinez-Urbistondo [a,k,ae], Lucas Tojal-Sierra [a,m], Carlos Muñoz-Bravo [af], Salvador Miralles-Gisbert [ag], Marian Martin [c], Antonio García-Ríos [a,q], Sara Castro-Barquero [a,r], José Carlos Fernández-García [a,s], José Manuel Santos-Lozano [a,t], F. Javier Basterra-Gortari [a,e], Liliana Gutiérrez-Carrasquilla [g,h], Patricia Guillem-Saiz [a,i], Alba Satorres [a,j], Itziar Abete [a,l], Carolina Sorto-Sanchez [a,m], Javier Díez-Espino [a,e], Nancy Babio [a,g], Montse Fitó [a,j], Josep A. Tur [a,b,c,*]

[a] CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III (ISCIII), 28029 Madrid, Spain
[b] Research Group on Community Nutrition & Oxidative Stress, University of Balearic Islands-IUNICS, 07122 Palma de Mallorca, Spain
[c] Health Research Institute of the Balearic Islands (IdISBa), 07120 Palma de Mallorca, Spain
[d] Faculty of Health Sciences,Catholic University of Avila, 05005 Avila, Spain
[e] University of Navarra, Department of Preventive Medicine and Public Health, IDISNA, 31008 Pamplona, Spain
[f] Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, USA
[g] Universitat Rovira i Virgili, Biochemistry and Biotechnology Department, Human Nutrition Unit, IISPV, Hospital Universitari de Sant Joan, 43201 Reus, Spain
[h] Unidad de Nutrición, Lípidos y Endocrinologia, Hospital Universitari de Sant Joan de Reus, Institut d'Insvestigacions Sanitàries Pere Virgili (IISPV), 43201 Reus, Spain
[i] Department of Preventive Medicine, University of Valencia, 46100 Valencia, Spain
[j] Unit of Cardiovascular Risk and Nutrition, Institut Hospital del Mar de Investigaciones Médicas Municipal d'Investigació Mèdica (IMIM), 08003 Barcelona, Spain
[k] Cardiometabolics Precision Nutrition Program, IMDEA Food, CEI UAM + CSIC, 28049 Madrid, Spain
[l] Department of Nutrition, Food Sciences, and Physiology, Center for Nutrition Research, University of Navarra, 31008 Pamplona, Spain
[m] Bioaraba Health Research Institute, Osakidetza Basque Health Service, Araba University Hospital, University of the Basque Country UPV/EHU, 48013 Vitoria, Gasteiz, Spain
[n] Department of Nursing, School of Health Sciences, University of Malaga, Institute of Biomedical Research in Málaga (IBIMA-University of Malaga), 29071 Málaga, Spain
[o] Instituto de Investigación Sanitaria y Biomédica de Alicante, ISABIAL-UMH, 03550 Alicante, Spain
[p] CIBER Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III (ISCIII), 28029 Madrid, Spain
[q] Lipids and Atherosclerosis Unit, Department of Internal Medicine, Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Reina Sofia University Hospital, University of Cordoba, 14004 Córdoba, Spain
[r] Department of Internal Medicine, IDIBAPS, Hospital Clinic, University of Barcelona, 08036 Barcelona, Spain
[s] Virgen de la Victoria Hospital, Department of Endocrinology, University of Málaga, 29010 Málaga, Spain
[t] Department of Family Medicine, Research Unit, Distrito Sanitario Atención Primaria Sevilla, 41013 Sevilla, Spain

Abbreviations: BMI, Body Mass Index; DPP-4, 4-dipeptidyl peptidase; DPP-4I, 4-dipeptidyl peptidase inhibitors; EMA, European Medicines Agency; FDA, Food and Drug Administration; GIP, gastric inhibitory polypeptide; GLM, General Liner Model; GLP-1, glucagon-like peptide; GLP-1RA, Glucagon-like drugs peptide-1 receptor agonists; HbA1c, glycosylated hemoglobin; MetS, Metabolic Syndrome; WC, waist circumference.

☆ Clinical Trial Registry number: The trial was registered in 2014 at the International Standard Randomized Controlled Trial (ISRCT; http://www.isrctn.com/ISRCTN89898870) with number 89898870.

* Correspondence to: Research Group on Community Nutrition and Oxidative Stress, University of the Balearic Islands & CIBEROBN, Guillem Colom Bldg, Campus, E-07122 Palma de Mallorca, Spain.

E-mail address: pep.tur@uib.es (J.A. Tur).

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[u] Institute for Biomedical Research, University of Las Palmas de Gran Canaria, 35016 Las Palmas, Spain
[v] Department of Preventive Medicine, University of Granada, 18071 Granada, Spain
[w] Institute of Biomedicine (IBIOMED), University of León, 24071 Leon, Spain
[x] Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge, Hospital Universitario de Bellvitge, 08907 Barcelona, Spain
[y] Department of Health Sciences, Center for Advanced Studies in Olive Grove and Olive Oils, University of Jaen, 23071 Jaen, Spain
[z] Department of Endocrinology and Nutrition, Instituto de Investigación Sanitaria San Carlos (IdISSC), 28040 Madrid, Spain
[aa] Department of Endocrinology, IDIBAPS, Hospital Clinic, University of Barcelona, 08036 Barcelona, Spain
[ab] Department of Endocrinology, Fundación Jiménez-Díaz University Hospital, 28040 Madrid, Spain
[ac] Nutritional Control of the Epigenome Group, Precision Nutrition and Obesity Program, IMDEA Food, CEI UAM + CSIC, 28049 Madrid, Spain
[ad] Lipid Clinic, Department of Endocrinology and Nutrition, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clínic, 08036 Barcelona, Spain
[ae] Internal Medicine Department, HM Sanchinarro, 28050 Madrid, Spain
[af] Division of Preventive Medicine and Public Health, University of Malaga, Institute of Biomedical Research in Málaga (IBIMA-University of Malaga), Málaga, Spain
[ag] Centro de Salud El Raval, 03203 Elche, Alicante, Spain

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ABSTRACT

Aims: To assess the comparative effects of glucagon-like peptide-1 receptor agonists (GLP-1RA), 4-dipeptidyl peptidase inhibitors (DPP-4I), and metformin treatment during one year on metabolic syndrome (MetS) components and severity in MetS patients.
Methods: Prospective study (n = 6165 adults) within the frame of PREDIMED-Plus trial. The major end-point was changes on MetS components and severity after one- year treatment of GLP-1RA, DPP-4I, and metformin. Anthropometric measurements (weight, height and waist circumference), body mass index (BM), and blood pressure were registered. Blood samples were collected after overnight fasting. Plasma glucose, glycosylated hemoglobin (HbA1c), plasma triglycerides and cholesterol were measured. Dietary intakes as well as physical activity were assessed through validated questionnaires.
Results: MetS parameters improved through time. The treated groups improved glycaemia compared with untreated (glycaemia Δ untreated: −1.7 mg/dL(± 13.5); Δ metformin: − 2.5(± 23.9) mg/dL; Δ DPP-4I: − 4.5(± 42.6); mg/dL Δ GLP-1RA: − 4.3(± 50.9) mg/dL; and HbA1c: Δ untreated: 0.0(± 0.3) %; Δ metformin: − 0.1(± 0.7) %; Δ DPP-4I: − 0.1(± 1.0) %; Δ GLP-1RA: − 0.2(± 1.2) %. Participants decreased BMI and waist circumference. GLP-1RA and DPP-4I participants registered the lowest decrease in BMI (Δ untreated: −0.8(± 1.6) kg/m^2; Δ metformin: − 0.8(± 1.5) kg/m^2; Δ DPP-4I: − 0.6(± 1.3) kg/m^2; Δ GLP-1RA: − 0.5(± 1.2) kg/m^2. and their waist circumference (Δ untreated: −2.8(± 5.2) cm; Δ metformin: − 2.6(± 15.2) cm; Δ DPP-4I: − 2.1(± 4.8) cm; Δ GLP-1RA: − 2.4(± 4.1) cm.
Conclusion: In patients with MetS and healthy lifestyle intervention, those treated with GLP-1RA and DPP-4I obtained better glycemic profile. Anthropometric improvements were modest.

1. Introduction

Incretin peptides, gastric inhibitory polypeptide (GIP) and glucagon-like peptide (GLP)−1 are secreted by enteroendocrine cells K and L, respectively [1,2]. They are part of an endogenous system involved in the physiological regulation of blood glucose. In patients with type 2 diabetes mellitus, a reduction in GLP has been observed, but not in GIP [3]. There is evidence that GLP-1 reduces inflammation, and GIP induces bone formation [1,4]. 4-Dipeptidyl peptidase (DPP-4) is a transmembrane glycoprotein aminopeptide that is widely expressed on several tissues, and can be measured in plasma [5]. DPP-4 inactivates GIP and GLP-1, which explains the short half-life of these in plasma [6].

Glucagon-like peptide-1 receptor agonists (GLP-1RA), which are resistant to degradation by the enzyme DPP-4, and 4-dipeptidyl peptidase inhibitors (DPP-4I) or gliptins are a new drugs to treat type 2 diabetes mellitus in adults, belonging to the therapeutic group of incretin-mimetics. GLP-1RA mimics the effects of the incretin hormone GLP-1 with a longer duration of action and a greater potency to reduce glucose [7]. Traditionally, all GLP-1RA were administered subcutaneously due to their low oral bioavailability. However, the Food and Drug Administration (FDA) lately approved an oral formulation of semaglutide [8]. In 2014 the FDA and in 2015 the European Medicines Agency (EMA) approved the use of liraglutide at doses of 3.0 mg for the pharmacological treatment of obesity or in the case of overweight patients with associated comorbidities [9].

DPP-4I increases the concentration of GLP-1 and GIP by inhibiting the activity of the DPP-4 enzyme, thus leading to an increase in insulin secretion from beta cells and a reduction in blood glucose [10]. Administered orally [11], it has a low incidence of hypoglycemia, decreases glycosylated hemoglobin (HbA1c) and it has neutral effect on body weight [10–13].

Metabolic syndrome (MetS), according to the International Diabetes Federation and the American Heart Association and National Heart, Lung and Blood Institute [14] is a condition in which a person sows three or more of the following factors: high glycaemia levels (>100 mg/dL), hypertension (>130/85 mmHg), raised triglyceride levels (>150 mg/dL), low high-density lipoprotein cholesterol levels (<40 mg/dL in men; <50 mg/dL in women), and abdominal obesity (waist circumference of >102 cm in men; >88 cm in women). Several pharmacologic treatments have been approved for some of the abovementioned conditions; however, up to date, no pharmacologic treatment has been approved to treat MetS as a whole. Main and most recommended treatment for MetS as a whole is a healthy lifestyle [15,16]. In addition to a lifestyle intervention, it is necessary to establish different pharmacological treatments for the management of MetS, so the use of drugs with multiple effects can be interesting to reduce possible drug interactions and expenses.

Lately there have been published reviews that have focused on the effect of GLP-1RA and DPP-4I on MetS [17,18]. However, there are limited studies on the efficacy of these drugs in the overall treatment of MetS in individuals with lifestyle intervention who had already instituted treatment before the start of such intervention.

The aim of this study was to assess the comparative effects of GLP-1RA, DPP-4I, and metformin treatment during one year on MetS components and severity in MetS patients.

2. Materials and methods

2.1. Study design

This is a prospective cohort analysis of data obtained between baseline and 1 year, within the frame of PREDIMED-Plus trial, a 6-year

parallel-group multicenter randomized trial. One of the two interventions was randomly assigned to each participant. Briefly, interventions were energy reduced Mediterranean diet with physical activity promotion and intensive behavioral support, centered around weight loss, and usual care as energy unrestricted Mediterranean diet without physical activity and less intensive behavioral support, without any aim on weight loss. Number 89898870 was assigned to the trial when it was registered at the International Standard Randomized Controlled Trial in 2014 (ISRCT; http://www.isrctn.com/ISRCTN89898870). Further information on study protocol can be found elsewhere [19] and at http://predimedplus.com/. The major endpoint of the current observational study was changes on MetS components and severity after one- year treatment of GLP-1RA, DPP-4I, and metformin.

2.2. Participants, recruitment, randomization, and ethics

Eligible participants were community-dwelling adult men aged 55–75 and women aged 60–75. Inclusion criteria were body mass index (BMI) between 27 and 40 kg/m^2, with at least 3 criteria of metabolic syndrome, according to the updated harmonized definition of the International Diabetes Federation and the American Heart Association and National Heart, Lung and Blood Institute as previously mentioned [14]. Exclusion criteria, as published elsewhere [19], were: a) inability or unwillingness to give informed consent, b) history of documented CVD, c) active cancer or a history of malignant tumors in the last 5 years; d) Inability to continue the recommended diet or PA; e) low predicted probability of changing eating habits (Prochaska and Hardly criteria); f) inability to follow scheduled visits; g) weight loss (> 5 kg) 6 months prior to visit selection; h) history of surgery to lose weight or intend to undergo bariatric surgery in the following 12 months; i) history of intestinal resection, inflammatory bowel disease, cirrhosis or liver failure; j) obesity of endocrine origin (with the exception of treated hypothyroidism); k) food allergy to MedDiet components; l) serious psychiatric disorders, m) severe condition with less 24 mo life expectancy, n) dependence on illicit drugs; and o) medication for weight loss in the last 6 months.

Between September 2013 and October 2016, 9677 adults were contacted, of which 6874 were eligible, included and randomized into the study, in a 1:1 ratio. Further details on randomization are available elsewhere [19]. Fig. 1 summarizes flow chart of study participants.

The study protocols followed the Declaration of Helsinki ethical standards and were approved by ethics committees of all participants, and within them, the Ethics Committee of Research of Balearic Islands (ref. CEIC-IB2251/14PI). All participating institutions approved the study protocol and procedures according to Declaration of Helsinki's ethical standards. All participants provided written informed consent.

2.3. Anti-diabetic drug intake assessment

Drug intake was asked to participants (including active pharmaceutical ingredient and dose). Moreover, participant's report was confirmed by clinical history. This information was obtained at baseline, 6 months and 1 year.

Antidiabetic treatment consistency during the first year was an inclusion criterion for the current study. For this purpose, 4 treatments were considered: 1) Permanent absence of diabetic treatment during the first year; 2) Permanent metformin treatment not combined with other drugs; 3) Permanent anti-diabetic treatment with DPP-4I alone or combined with other anti-diabetic drugs; 4) Permanent anti-diabetic treatment with GLP-1RA alone or combined with other anti-diabetic drugs. Participants were classified into one of the mentioned treatments. Concomitant antidiabetic treatments for the DPP-4I and GLP-1RA were mainly metformin, insulin, and sulfonylurea drugs.

Participants who, for the studied period (baseline, 6 months and 1 year), did not maintain their treatment within one of the above-mentioned categories were excluded. Treatment was asked directly to participants, and further confirmed by clinical history. For example, participants entering the study taking metformin alone that changed their treatment at 6 months (or 1 year) by GLP-1RA alone or stopped taking drugs for diabetes were excluded from the study. Neither dosage changes nor changes in active principle within described categories were exclusion criteria for the present study.

Due to this criterion, 709 participants were excluded. Final sample size was of 6165 participants, which distributed into: (a) 4963 participants that did not take any drugs for diabetes management, because they were not diabetic; (b) 756 participants treated for diabetes with metformin; (c) 397 participants treated for diabetes with DPP-4I alone or combined with other antidiabetic drugs; and (d) 49 participants treated for diabetes with GLP-1RA alone or combined with other antidiabetic drugs. Effects of GLP-1RA and DPP-4I should be present even when they are combined with other drugs [20–22].

2.4. Metabolic Syndrome assessment

Anthropometric measurements were performed in duplicate by registered and trained dietitians. A wall-mounted stadiometer and high-quality electronic calibrated scales were used to measure height and weight, respectively. Height was measured as previous guidelines [23]. Body Mass Index (BMI) was calculating dividing weight in kilograms by the square of height in meters. Waist circumference (WC) was measured halfway between the iliac crest and the last rib, using an anthropometric tape.

A validated semi-automatic oscillometer (Omron HEM-705CP, Lake Forest, IL, USA) was used to assess blood pressure. Measures were taken in triplicate, after 5-minute siting rest. One minute was waited between

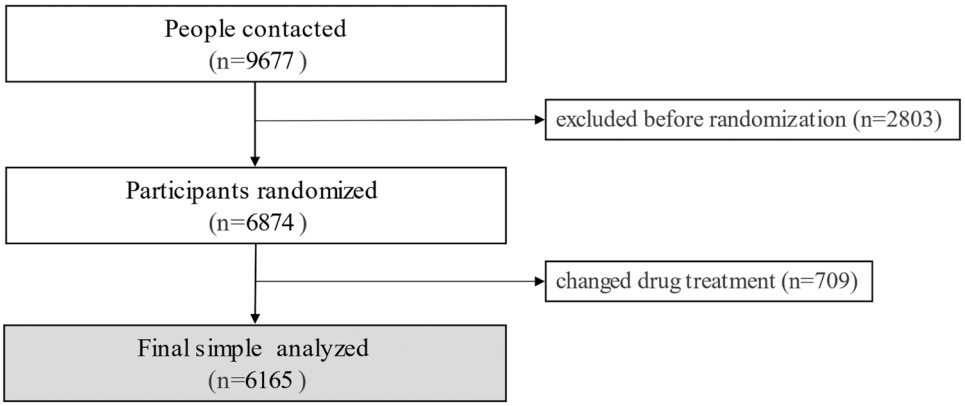

Fig. 1. Flow chart of study participants.

measurements. Cuff was adjusted to the circumference of the upper arm. Measurements were performed in the arm registering the highest diastolic blood pressure in the first selection visit. All measurements of a participant were performed in the same arm for the whole study.

Blood samples were collected after overnight fasting (at least 8 h) and analyzed in local laboratories. Standard enzymatic methods were used to perform biochemical blood sample analysis. Fasting plasma glucose, glycosylated hemoglobin (HbA1c), fasting plasma triglycerides, HDL and total fasting cholesterol were measured. LDL cholesterol was calculated through the Friedewald formula. Further information on blood sample analysis is available elsewhere [19].

Metabolic syndrome severity score is obtained through blood triglycerides, HDL-cholesterol, blood glucose, waist circumference and systolic and diastolic blood pressure [24].

2.5. Other lifestyle related variables (sociodemographic, diet and physical activity data)

Dietary intake was obtained by registered dietitians at baseline, 6 months and 1 year follow up. For that purpose, a previously validated for the Spanish population semi quantitative 143-item food frequency questionnaire [25] was used.

Mediterranean diet adherence was obtained from the 17-item Mediterranean diet questionnaire by registered dietitians. It is a modified version of the previously validated questionnaire used in the PREDIMED trial [19].

Physical activity was assessed by the validated Minnesota-REGICOR short physical activity questionnaire [26], while sedentary behaviors were assessed by the validated Spanish version of the nurses' health study questionnaire [27].

All participants provided sociodemographic information.

2.6. Statistical analyses

SPSS statistical software package version 27.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis. Data are shown as mean and standard deviation (SD). Prevalence is shown as sample size and percentage. Differences among groups for baseline age were tested with one-way ANOVA, with Bonferroni's post-hoc analysis. Differences in baseline prevalence among groups were tested using $\chi 2$ (all p-values are two-tailed).

Changes on lifestyle related variables, metabolic syndrome components and metabolic syndrome severity score according to anti-diabetic drugs intake during the first year of the intervention were analyzed by the Generalized Linear Model (GLM). The effect of the interaction was examined by using repeated-measures ANCOVA with 2 factors: time (baseline, 6 months and 1 year) as repeated measure, group (3 groups abovementioned) and their interactions, with gender and changes in BMI. Adherence to Mediterranean Diet and physical activity analysis were furthermore adjusted by change in energy intake. Metabolic syndrome related variables were furthermore adjusted by adherence to Mediterranean Diet and each component specific drug intake (for overweight, hypertension or dyslipidemia). BMI and waist circumference analysis were adjusted by change in energy intake, rather than changes in BMI. Differences in the effects of each group within and between groups were obtained through the Bonferroni post-hoc test. Furthermore, differences among groups at 6 and 12 months (dependent variable) were assessed by one-way ANCOVA, after additional adjustment by the baseline values of the same variable (data not shown). If p-value (2 tailed) was lower than 0.05, results were considered statistically significant.

Generalized Lineal Model through linear regression models were fitted to assess the association between evolution of metabolic syndrome components and antidiabetic drug intake (dependent variable). The group not pharmacologically treated for diabetes was established as the reference. Analysis was adjusted by gender, age, specific drug intake (for overweight, hypertension or dyslipidemia) and changes in energy intake and expenditure. Data on linear regression are shown as β coefficient (95 % confidence intervals). P-value lower than 0.05 was considered statistically significant.

3. Results

3.1. Sociodemographic characteristics of the participants

Table 1 shows sociodemographic characteristics and prevalence of metabolic syndrome components among participants. No differences in sociodemographic characteristics were found except for gender distribution. More men than women were treated for diabetes, in either of the treated groups.

All participants (100 %) in the 3 treated groups were diabetic according to the Joint Interim Statement definition of MetS [14]. No differences in prevalence of high blood pressure and abdominal obesity were found among groups. However, a higher prevalence of dyslipidemia (triglyceridemia and low HDL-cholesterolemia) was found in GLP-1IRA treatment, compared to the other groups.

Treatment with DPP-4I and GLP-1RA could be provided as a monotherapeutic treatment or combined with other drugs. Drugs used together with DPP-4I and GLP-1RA were similarly used among both groups.

3.2. Changes in lifestyle factors through the first year of the trial

Changes in lifestyle factors through the first year of the trial are available in Table 2. As much as all groups reduced their energy intake during the first 6 months and maintained their caloric intake after that, no time*group interactions were fund for energy intake (Δ untreated: −188.2 Kcal/day (± 574.7); Δ metformin: 188.8 Kcal/day (± 552.4); Δ DPP-4I: − 144.6 Kcal/day (± 567.6); Δ GLP-1RA: − 171.0 Kcal/day (± 551.0).). On the other hand, Mediterranean diet adherence, while it improved for all participants through time, the improvement was lower in the metformin-treated group (Δ Untreated: 3.3 (± 3.3); Δ metformin: 2.9 (± 3.2); Δ DPP-4I: 3.3 (± 3.0); Δ GLP-1RA: 3.7 (± 2.7).). Physical activity increased through time in the whole cohort, except in GLP-1RA treated participants, who maintained their physical activity through the period studied. No time*group interactions have been found. However, the group treated with GLP-1RA and DPP-4I registered the lower physical activity levels at 1 year follow up (Δ untreated: 523.4 (± 2501.2); Δ metformin: 593.6 (± 2492.5); Δ DPP-4I: 364.5 (± 2207.3); Δ GLP-1RA: 76.6 (± 1834.1).

3.3. Six months and One-year changes in Metabolic Syndrome components and in overall metabolic syndrome severity score

Table 3 shows 6 months and 1-year changes in MetS components and in overall MetS severity score. The not treated group registered the lowest improvements on glycemic profile (glycemia Δ untreated: −1.7 mg/dL (± 13.5); Δ metformin: − 2.5 mg/dL (± 23.9); Δ DPP-4I: − 4.5 mg/dL (± 42.6); Δ GLP-1RA: − 4.3 mg/dL (± 50.9). and HbA1c: Δ untreated: 0.0 % (± 0.3); Δ metformin: − 0.1 % (± 0.7); Δ DPP-4I: − 0.1 % (± 1.0); Δ GLP-1RA: − 0.2 % (± 1.2).). All participants decreased their BMI and waist circumference through the period studied. However, participants in the GLP-1RA and DPP-4I group registered the lowest decrease in their BMI (Δ untreated: −0.8 kg/m2 (± 1.6); Δ metformin: − 0.8 kg/m^2 (± 1.5); Δ DPP-4I: − 0.6 kg/m^2 (± 1.3); Δ GLP-1RA: − 0.5 kg/m^2 (± 1.2).) and their waist circumference (Δ untreated: −2.8 cm (± 5.2); Δ metformin: − 2.6 cm (± 15.2); Δ DPP-4I: − 2.1 cm (± 4.8); Δ GLP-1RA: − 2.4 cm (± 4.1).). Improvements through time in systolic and diastolic blood pressures were registered, however, no time*group interactions were found. Through all the studied period (baseline 6 and 12 months), total, LDL and HDL cholesterol levels were higher while triglyceride levels were lower in the

Table 1
Baseline sociodemographic characteristics according to antidiabetic drug intake.

	No treatment § ($n = 4963$) Mean (SD)	Metformin treatment § ($n = 756$) Mean (SD)	DPP-4I treatment § ($n = 397$) Mean (SD)	GLP-1RA treatment § ($n = 49$) Mean (SD)	p-value ‡
Basal age (years)	64.9 (4.9)	65.2 (4.8)	65.0 (5.0)	63.6 (4.9)	0.116
	n(%)	n(%)	n(%)	n(%)	
Gender (female)	2504 (50.5)	337 (44.6)	173 (43.6)	21 (42.9)	0.002
Group (hypocaloric MedDiet)	2521 (50.8)	363 (48.0)	203 (51.1)	26 (53.1)	0.526
MetS components					
High blood pressure	4550 (91.7)	700 (92.6)	369 (92.9)	45 (91.8)	0.708
Hyperglycaemia	3315 (66.8)	756 (100.0)	397 (100.0)	49 (100.0)	< 0.001
Hypertriglyceridemia	2809 (56.6)	371 (49.1)	219 (55.2)	33 (67.3)	< 0.001
Low HDL-cholesterol	2070 (41.7)	306 (40.5)	197 (49.6)	35 (71.4)	< 0.001
Abdominal obesity	4763 (96.0)	727 (96.2)	388 (97.7)	49 (100.0)	0.167
Smoking habit					0.210
Current smoker	605 (12.2)	92 (12.2)	47 (11.9)	7 (14.3)	
Former smoker	2112 (42.7)	350 (46.4)	177 (44.9)	27 (55.1)	
Never smoked	2230 (45.1)	312 (41.4)	170 (43.1)	15 (30.6)	

Abbreviations: MedDiet. Mediterranean Diet. SD. Standard deviation. § Treatment for diabetes: 1) no pharmacological treatment for diabetes. 2) Metformin treatment. 3) DPP-4I treatment 4) GLP-1RA treatment. ‡ Living alone regardless of marital status. Hyperglycaemia according to the Joint Interim Statement definition of MetS (fasting glucose ≥100 mg/dL). *Differences in means between groups were tested by one-way ANOVA and Bonferroni's post-hoc. Differences in prevalence's across groups were examined using χ^2.

Table 2
Lifestyle related variables according to antidiabetic drug intake.

		No treatment § ($n = 4963$) Mean (SD)	Metformin treatment § ($n = 756$) Mean (SD)	DPP-4I treatment § ($n = 397$) Mean (SD)	GLP-1RA treatment § ($n = 49$) Mean (SD)	*Time* group*
Energy intake (Kcal/day)	Baseline	2435.2 (635.1)[a]	2350.8 (572.2)[a]	2387.5 (572.1)	2331.5 (608.7)	
	6 months	2252.5 (486.1) *[a]	2181.3 (451.3) *[a,c]	2226.5 (461.6) *	2106.4 (502.5) *[c]	
	1 year	2246.0 (483.7)[a]	2177.4 (462.5)[a]	2237.5 (503.7)	2175.0 (517.3)	
	Δ	-188.2 (574.7) ⁂	-188.8 (552.4) ⁂	-144.6 (567.6) ⁂	-171.0 (551.0)	0.885
17 item MedDiet	Baseline	8.4 (2.7)	9.0 (2.6)	8.5 (2.6)	8.1 (2.3)	
	6 months	11.5 (2.9) *	11.6 (2.7) *	11.5 (2.7) *	10.7 (2.9) *	
	1 year	11.7 (2.9) ⁑	11.8 (2.8) ⁑	11.7 (2.7)	11.6 (2.5) ⁑	
	Δ	3.3 (3.3) ⁂[g]	2.9 (3.2) ⁂[g,j]	3.3 (3.0) ⁂[j]	3.7 (2.7) ⁂	< 0.001
Total PA † (METs)	Baseline	2488.6 (2310.1)	2413.1 (2183.3)	2303.5 (2187.2)	2370.6 (2794.5)	
	6 months	2930.8 (2457.6) *	2953.2 (2538.5) *	2821.3 (2343.3) *	2259.0 (2284.4)	
	1 year	3050.5 (2496.4) ⁑[b]	3014.1 (2459.1)	2708.2 (2266.3)[b]	2471.1 (2469.6)	
	Δ	523.4 (2501.2) ⁂	593.6 (2492.5) ⁂	364.5 (2207.3) ⁂	76.6 (1834.1)	0.527

Abbreviations: Δ. Change between baseline and 1 year. 17 item MedDiet. 17-item Mediterranean dietary questionnaire. PA. Physical activity. MET. Metabolic equivalent of task. SD. Standard deviation. **§ Treatment for diabetes**: 1) no pharmacological treatment for diabetes. 2) Metformin treatment. 3) DPP-4I treatment 4) GLP-1RA treatment. Data analysed by two-way repeated measures ANCOVA adjusted by gender and change in BMI. Adherence to MedDiet and physical activity analysis were furthermore adjusted by change in energy intake. Different letters indicate statistically significant differences ($p < 0.05$) between groups (a, b, c, d, e, f), between time (*Baseline-6 months; ⁑6 months-1 year; ⁂Baseline-1 year.) and between time*group interaction (g, h, i, j, k, l) by the Bonferroni post-hoc test ($p < 0.05$).

untreated group than in the other groups. On the other hand, triglyceride levels were higher and total, LDL and HDL cholesterol levels were lower in the GLP-1RA and DPP-4I treated groups. MetS severity reduced similarly for all groups. Neither statistical nor clinically relevant differences were found in metabolic syndrome severity among groups.

3.4. Association of metabolic syndrome components and antidiabetic drug intake

Table 4 shows beta-coefficients (β) (95 % confidence interval) for associations between drug intake and changes in metabolic syndrome components and MetS severity adjusted by potential confounders. All treatments related to improvements in glycemic profile (HbA1c: metformin: −0.07 (−0.12 to 0.03); DPP-4I: − 0.10 (−0.15 to 0.04); GLP-1RA: − 0.18 (−0.33 to 0.04); glycaemia: metformin: − 0.83 (−2.51, 0.84); DPP-4I: − 2.27 (−4.50 to 0.03); GLP-1RA: − 2.90 (−8.77, 2.97)). However, DPP-4I treatment registered the less desirable anthropometric evolution, as they registered lower decreases in anthropometric variables, when they compared to the untreated group (BMI: metformin: −0.04 (−0.16, 0.09); DPP-4I: 0.19 (0.03, 0.35); GLP-1RA:0.32 (−0.12, 0.77); waist circumference: metformin: 0.23 (−0.18, 0.64); DPP-4I: 0.67 (0.13, 1.22); GLP-1RA:0.24 (−1.23, 1.71)). No statistically significant results were obtained for the other metabolic syndrome components or in the MetS Severity Score.

4. Discussion

4.1. Changes in lifestyle factors through the first year of the trial

The results of the current study showed that all groups decreased their energy intake at six months and maintained it at one year. However, no significant time*group interactions were observed. From the clinical point of view, it should be noted that the subjects who decreased their energy intake the least at one year of the intervention were those treated with DPP-4I. In this sense, Rotondo et al. [28] in their study on healthy adults observed that vildagliptin (DPP-4I) did not decrease food intake or total caloric intake compared to placebo. DeFronzo et al. [29] compared the effects on gastric emptying and caloric intake of sitagliptin (DPP-4I) and exenatide (GLP-1RA) in patients with type 2 diabetes mellitus treated with metformin. The authors concluded that only exenatide slowed gastric emptying and reduced total caloric intake. Therefore, in the current study, reduction of total caloric intake observed in the group treated with DPP-4I, although lower than in the other groups, could be due exclusively to the lifestyle modification

Table 3
Metabolic syndrome components and metabolic syndrome severity score according to antidiabetic drug intake.

		No treatment § ($n = 4963$)	Metformin treatment § ($n = 756$)	DPP-4I treatment § ($n = 397$)	GLP-1RA treatment § ($n = 49$)	*Time* group*
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Glucose ǂ	Baseline	104.2 (16.4)^{a,b,c}	126.1 (23.6)^{a,d,e}	151.7 (43.2)^{b,d}	147.6 (47.3)^{c,e}	
(mg/dL)	6 months	102.0 (15.5) ^{*a,b,c}	124.0 (23.8) ^{*a,d,e}	147.0 (45.4) ^{*b,d}	146.5 (55.4)^{c,e}	
	1 year	102.4 (16.1)^{a,b,c}	123.5 (26.9)^{a,d,e}	146.4 (41.5)^{b,d}	143.2 (40.5)^{c,e}	
	Δ	-1.7 (13.5) ⁂^{h}	-2.5 (23.9) ⁂	-4.5 (42.6) ⁂^{h}	-4.3 (50.9)	0.002
HbA1c (%)	Baseline	5.8 (0.5)^{a,b,c}	6.5 (0.7)^{a,d,e}	7.2 (1.2)^{b,d}	7.4 (1.3)^{c,e}	
	6 months	5.8 (0.5) ^{*a,b,c}	6.4 (0.8) ^{*a,d,e}	7.0 (1.2) ^{*b,d}	7.3 (1.2) ^{*c,e}	
	1 year	5.8 (0.5)^{a,b,c}	6.4 (0.8)^{a,d,e}	7.1 (1.1)^{b,d}	7.3 (1.1)^{c,e}	
	Δ	0.0 (0.3) ⁂^{g,h,i}	-0.1 (0.7) ⁂^{g}	-0.1 (1.0) ⁂^{h}	-0.2 (1.2) ⁂^{i}	< 0.001
BMI	Baseline	32.5 (3.4)^{c}	32.6 (3.5)^{e}	32.4 (3.4)^{f}	34.8 (3.2)^{c,e,f}	
(kg/m^2)	6 months	31.7 (3.6) ^{*c}	32.0 (3.6) ^{*e}	31.8 (3.5) ^{*f}	34.2 (3.2) ^{*c,e,f}	
	1 year	31.6 (3.6) ǂ^{c}	31.8 (3.7) ǂ^{e}	31.8 (3.6)^{f}	34.3 (3.2)^{c,e,f}	
	Δ	-0.8 (1.6) ⁂	-0.8 (1.5) ⁂^{j,k}	-0.6 (1.3) ⁂^{j}	-0.5 (1.2)^{k}	0.001
Waist	Baseline	106.9 (9.7)^{a,b,c}	108.6 (9.5)^{a,e}	109.1 (8.7)^{b,f}	117.9 (8.4)^{c,e,f}	
circumference	6 months	104.4 (9.8) ^{*a,b,c}	106.6 (9.8) ^{*a,e}	107.3 (9.0) ^{*b,f}	115.1 (8.9) ^{*c,e,f}	
(cm)	1 year	104.0 (10.0) ǂ^{a,b,c}	106.0 (9.8) ǂ^{a,e}	106.9 (9.2)^{b,f}	115.7 (8.5)^{c,e,f}	
	Δ	-2.8 (5.2) ⁂^{h}	-2.6 (5.2) ⁂^{j}	-2.1 (4.8) ⁂^{h,j}	-2.4 (4.1) ⁂	0.015
Systolic blood	Baseline	139.2 (16.8)	140.0 (16.5)	140.3 (17.5)	138.6 (12.1)	
pressure	6 months	136.7 (16.8) *	137.5 (16.8) *	139.3 (16.9)	136.6 (12.1)	
(mmHg)	1 year	136.0 (16.5) ǂ	136.5 (16.6)	138.6 (15.5)	134.3 (15.1)	
	Δ	-3.3 (15.5) ⁂	-3.2 (14.3)	-1.6 (14.5)	-4.4 (14.3)	0.685
		No treatment § ($n = 4963$)	Metformin treatment § ($n = 756$)	DPP-4I treatment § ($n = 397$)	GLP-1RA treatment § ($n = 49$)	*Time* group*
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Diastolic	Baseline	81.1 (9.9)^{c}	80.8 (10.2)^{e}	79.7 (9.6)^{f}	76.0 (9.8)^{c,e,f}	
blood	6 months	79.6 (9.8) ^{*c}	79.2 (9.8) *	78.7 (9.4) *	76.3 (8.6)^{c}	
pressure	1 year	79.2 (9.8) ǂ^{c}	78.6 (9.7)^{e}	78.4 (8.8)	75.0 (10.2)^{c,e}	
(mmHg)	Δ	-1.9 (8.5) ⁂	-2.2 (8.2) ⁂	-1.4 (7.8) ⁂	-0.2 (9.3)	0.763
Triglycerides ǂ	Baseline	149.6 (74.0)^{b,c}	147.2 (68.5)^{d,e}	166.7 (95.5)^{b,d,f}	210.0 (133.5)^{c,e,f}	
(mg/dL)	6 months	139.3 (66.6) ^{*b,c}	144.6 (75.3)^{e}	159.3 (97.0)^{b,f}	199.5 (110.2)^{c,e,f}	
	1 year	140.9 (69.7)^{b,c}	142.8 (69.6)^{d,e}	161.5 (93.8)^{b,d,f}	190.0 (105.4)^{c,e,f}	
	Δ	-8.0 (67.5) ⁂^{g}	-3.5 (60.3)^{g}	-4.8 (78.7)	-22.7 (68.1) ⁂	0.011
Total	Baseline	203.5 (36.5)^{a,b,c}	180.6 (33.1)^{a,d}	175.6 (33.6)^{b,d}	168.8 (38.2)^{c}	
cholesterol ǂ	6 months	202.1 (36.0) ^{*a,b,c}	180.8 (33.7)^{a,d}	172.2 (32.7)^{b,d}	172.8 (35.6)^{c}	
(mg/dL)	1 year	200.8 (35.8) ǂ^{a,b,c}	178.9 (34.9)^{a}	172.9 (42.2)^{b}	172.3 (37.6)^{c}	
	Δ	-2.6 (32.0) ⁂	-1.4 (30.1)	-1.7 (39.8)	3.3 (28.5)	0.544
HDL-	Baseline	49.0 (11.9)^{a,b,c}	46.9 (10.9)^{a,e}	44.7 (11.4)^{b,f}	39.1 (10.2)^{c,e,f}	
cholesterol ǂ	6 months	50.4 (12.1) ^{*a,b,c}	48.4 (11.8) ^{*a,e}	45.9 (11.6) ^{*b,f}	39.8 (8.4)^{c,e,f}	
(mg/dL)	1 year	50.5 (11.9)^{a,b,c}	47.8 (11.5)^{a,e}	46.2 (11.9)^{b,f}	40.7 (9.8)^{c,e,f}	
	Δ	1.5 (7.5) ⁂	1.1 (6.6) ⁂	1.2 (6.7) ⁂	1.3 (5.4)	0.811
LDL-	Baseline	125.3 (31.6)^{a,b,c}	105.1 (28.4)^{a,d,e}	98.9 (27.8)^{b,d}	89.7 (31.9)^{c}	
cholesterol ǂ	6 months	124.4 (31.4)^{a,b,c}	104.5 (29.4)^{a,d}	94.5 (25.4)^{b,d}	93.8 (32.8)^{c}	
(mg/dL)	1 year	122.8 (31.1) ǂ^{a,b,c}	103.7 (30.2)^{a,d}	94.7 (26.5)^{b,d}	91.7 (29.9)^{c}	
	Δ	-2.4 (27.6) ⁂	-1.4 (26.0)	-3.8 (24.2)	2.9 (23.6)	0.712
Metabolic Sdr	Baseline	3.2 (1.3)^{a,b,c}	3.7 (1.4)^{a,d,e}	4.5 (1.5)^{b,d,f}	5.0 (1.5)^{c,e,f}	
Severity	1 year	2.8 (1.4)^{a,b,c}	3.3 (1.4)^{a,d,e}	4.1 (1.5)^{b,d}	4.6 (1.5)^{c,e}	
Score	Δ	-0.4 (1.2) ⁂	-0.4 (1.2) ⁂	-0.4 (1.4) ⁂	-0.4 (1.4) ⁂	0.846

Abbreviations: Δ. Change between baseline and 1 year. BMI: Body mass index. HbA1c. glycosylated haemoglobin. HDL-cholesterol. High density lipoprotein cholesterol. LDL-cholesterol. Low density lipoprotein cholesterol. MetS. Metabolic Syndrome. SD. Standard deviation. **§ Treatment for diabetes**: 1) no pharmacological treatment for diabetes. 2) Metformin treatment. 3) DPP-4I treatment 4) GLP-1RA treatment. ǂ Measured on overnight fasting peripheral blood samples. Data analysed by two-way repeated measures ANCOVA adjusted by gender, Mediterranean diet adherence, change in BMI, and specific drug intake (for overweight, hypertension or dyslipaemia). BMI and waist circumference analysis were adjusted by change in energy intake, rather than changes in BMI. Different letters indicate statistically significant differences ($p < 0.05$) between groups (a, b, c, d, e, f), between time (*Baseline-6 months; ǂ6 months-1 year; ⁂Baseline-1 year.) and between time*group interaction (g, h, i, j, k, l) by the Bonferroni post-hoc test ($p < 0.05$).

program applied. Furthermore, the scientific literature showed homogeneous results of GLP-1RA on the reducing effects of appetite, eating pleasure and total caloric intake [30–32]. In the current study, subjects treated with GLP-1RA showed a slightly smaller reduction in total caloric intake than those not treated and those treated with metformin.

Adherence to the Mediterranean diet improved in all groups, with significant time*group interactions observed. The most improved adherence to the Mediterranean diet was observed in participants treated with GLP-1RA, and the one those treated with metformin. This has clinical relevance, as greater adherence to the Mediterranean diet, there was better glycemic control in diabetic patients [33].

Physical activity increased over time across the cohort, except for participants treated with GLP-1RA, who maintained their level of physical activity throughout the study period. No time*group interactions were found. This aspect is also important from a clinical point of view, since regular physical activity is a main component in the treatment of type 2 diabetes. [33].

It should be noted that the subjects treated with GLP-1RA were those with higher BMI and waist circumference at the beginning of the study. This may partly explain the fact that they were those who lower decreased their overall energy intake, and lower increased their physical activity from baseline.

4.2. Six months and One-year changes in Metabolic Syndrome components and in overall metabolic syndrome severity score

4.2.1. Effects on glycemic profile

All participants in the current study improved their glycaemia levels, with the smallest decrease in the untreated group. Although HbA1c levels improved in all groups except the untreated, improvements were

Table 4
Association of metabolic syndrome components and antidiabetic drug intake.

	§No treatment ($n = 4963$) β (95 % CI)	Metformin treatment § ($n = 756$) β (95 % CI)	DPP-4I treatment § ($n = 397$) β (95 % CI)	GLP-1RA treatment § ($n = 49$) β (95 % CI)
Glucose (mg/dL)	0.00 (ref.)	-0.83 (−2.51, 0.84)	-2.27 (−4.50,−0.03)*	-2.90 (−8.77, 2.97)
HbA1c (%)	0.00 (ref.)	-0.07 (−0.12,−0.03)*	-0.10 (−0.15,−0.04)*	-0.18 (−0.33,−0.04)*
BMI (kg/m^2)	0.00 (ref.)	-0.04 (−0.16, 0.09)	0.19 (0.03–0.35)*	0.32 (−0.12, 0.77)
Waist (cm)	0.00 (ref.)	0.23 (−0.18, 0.64)	0.67 (0.13–1.22)*	0.24 (−1.23, 1.71)
SBP (mmHg)	0.00 (ref.)	0.06 (−1.18, 1.30)	1.31 (−0.33, 2.94)	-1.25 (−5.64, 3.14)
DBP (mmHg)	0.00 (ref.)	-0.26 (−0.95, 0.42)	0.48 (−0.42, 1.38)	1.66 (−0.76, 4.08)
Triglycerides (mg/dL)	0.00 (ref.)	3.57 (−0.38, 7.51)	0.97 (−4.34, 6.29)	-6.17 (−20.94, 8.60)
Total chol. (mg/dL)	0.00 (ref.)	1.63 (−0.98, 4.25)	-1.28 (−4.80, 2.24)	2.52 (−7.25, 12.30)
HDL-chol. (mg/dL)	0.00 (ref.)	-0.32 (−0.94, 0.30)	-0.40 (−1.23, 0.44)	0.31 (−2.01, 2.62)
LDL-chol. (mg/dL)	0.00 (ref.)	1.25 (−1.08, 3.58)	-1.09 (−4.23, 2.05)	3.34 (−5.37, 12.06)
MetS Severity Score	0.00 (ref.)	-0.03 (−0.13, 0.08)	0.06 (−0.08, 0.20)	-0.03 (−0.38, 0.33)

Abbreviations: β. β coefficient. CI. Confidence Interval. BMI: Body mass index. HbA1c. glycosylated haemoglobin. SBP. Systolic blood pressure. DBP. Diastolic blood pressure. Total-chol. Total cholesterol. LDL-chol. Low density lipoprotein cholesterol. HDL-chol. High density lipoprotein cholesterol. MetS. Metabolic Syndrome. **§Treatment for diabetes**: 1) no pharmacological treatment for diabetes. 2) Metformin treatment. 3) DPP-4I treatment 4) GLP-1RA treatment. *p-value < 0.05. Analysis was adjusted by gender, age, specific drug intake (for overweight, hypertension or dyslipidaemia) and changes in energy intake and expenditure.

modest. The subjects who most decreased plasma glucose levels and HbA1c were those treated with DPP-4I or GLP-1RA. Significant time*-group interactions were observed. A similar reduction in plasma glucose and HbA1c was observed in participants treated with either GLP-1RA or DPP-4I.

The scientific literature showed that the presence of MetS may influence the glycemic response to DPP-4I. Thus, a clinical trial conducted by Fadini et al. [34], in which patients treated with exenatide (GLP-1RA) or DPP-4I were prospectively followed, dividing subjects into two groups according to the presence or not of MetS, patients receiving exenatide showed a greater reduction in HbA1c if they had Mets, while patients receiving DPP-4I showed a smaller reduction if they had MetS. Accordingly, clinical trials in MetS patients treated with liraglutide (GLP-1RA) showed a significant reduction in glucose levels. [35].

Regarding the effects of the interaction between intervention on lifestyle/pharmacotherapy on glycemic control in patients with type 2 diabetes mellitus., clinical trials conducted by Apovian et al. [36] and Moretto et al. [37] showed better glycemic control when a lifestyle modification program was combined with GLP-1RA. However, these clinical trials lasted six months and the participants did not have pharmacological treatment for diabetes mellitus before the intervention.

Hemmer et al. [38] conducted a clinical trial on the evolution of HbA1c over a four-year period in patients with type 2 diabetes mellitus treated with exenatide concluded that the beneficial effects of GLP-1RA on HbA1c reached a plateau after the first year of treatment; these benefits were maintained for the next four years in only one-third of patients. However, these results [38] regarding HbA1c should be interpreted with caution, since a high percentage of subjects abandoned the GLP-1RA treatment, and only a subgroup of 40 patients were followed for four years, out of the 131 that formed the final sample. A systematic review conducted by Esposito et al. [39] in which clinical trials with a minimum duration of 19 months were included, showed that the decrease in HbA1c at the end of DPP-4I treatment was significantly lower than intermediate points. This may partly explain the results of the current study, which shows the greatest decrease in HBA1c in the first six months of treatment.

4.2.2. *Effects on body mass index and waist circumference*

All participants decreased their BMI and waist circumference throughout the current study period, and significant time*group interactions were observed. Subjects treated with GLP-1RA showed greater decrease in waist circumference than those treated with DPP-4I; while in the BMI the reduction was similar in the two groups.

A previous clinical trial [36] in overweight or obese patients with type 2 diabetes mellitus introduced a lifestyle modification program plus exenatide (GLP-1RA) versus lifestyle modification program plus placebo, showed greater weight reduction in subjects receiving exenatide plus lifestyle modification. However, in this trial the follow-up of patients was done for six months, while in the current study, patients were followed for one year. In this sense, in the clinical trial conducted by Hemmer et al. [38], the results showed that, in the total sample, that is, both in the subjects who continued with the pharmacological treatment with GLP-1RA and those who abandoned it, the reduction in weight and BMI continued up to four years after the start of follow-up.

Regarding DPP-4I, the data available reflect a null effect of these drugs on body weight [40]. In a previous clinical trial [41], in which patients with type 2 diabetes mellitus and coronary artery disease were followed for six months, with the aim of comparing the effects of dapagliflozin (SGLT2 inhibitor) with those of vildagliptin (DPP-4I) on cardiometabolic parameters, the authors reported a decrease in weight and BMI significant in the SGLT2 inhibitor group, while in the DPP-4I group there was a significant increase in these parameters, with no differences in waist circumference observed in either group.

Several clinical trials compared the efficacy of GLP-1RA and DPP-4I on weight reduction, consistently showing better GLP-1RA performance. [42]. A study conducted with a cohort of U.S. patients who were prescribed these drugs in the clinic, and in which one-year follow-up was made, those patients with greater adherence to GLP-1RA treatment lose more weight, but in the case of DPP-4I weight loss was independent of adherence to pharmacological treatment [43].

On waist circumference, there were clinical trials showing that GLP-1 RA were more effective than DPP-4I, showing the latter negligible effects on waist circumference and BMI while resulting in slight weight gain [44]. Therefore, BMI and waist circumference reduction in DPP-4I could be directly related to the applied lifestyle intervention.

4.2.3. *Effects on the lipid profile*

Triglyceride levels decreased in all groups, and was greatest in participants treated with GLP-1RA. Total cholesterol and LDL cholesterol decreased in all groups, except in the GLP-1RA treated which increased slightly. HDL cholesterol increased in all groups. Thirty-three GLP-1RA users of current study had hypertriglyceridemia, and it should be considered that DDP-4 inhibitors and GLP-1 agonists were associated with increased risk of acute pancreatitis [45], despite achieving normal triglyceride levels is important to prevent recurrent episodes of acute pancreatitis [46].

Regarding the effects of GLP-1RA on HDL cholesterol, an analysis of a cohort of patients with type 2 diabetes mellitus and associated comorbidities on GLP-1RA treatment showed minimal change in HDL cholesterol [47]. Also, a meta-analysis on the effects of GLP-1RA on lipid profile in patients with type 2 diabetes mellitus did not find improvement in HDL-cholesterol levels [48]. Regarding the effects of GLP-1RA

on total cholesterol and LDL cholesterol, findings of the existing scientific literature match with those obtained in the current study, but not in relation to triglycerides [18], although it is noteworthy the fact that, in the current study, the subjects treated with GLP-1RA showed higher triglyceride levels at the beginning of the study.

In a meta-analysis whose objective was to compare the effects on the lipid profile of the different pharmacological treatments in patients with type 2 diabetes mellitus, the results showed that DPP-4I and standard therapy had no significant effect on lipid levels. [49]. Current results contrast with the meta-analysis, as they show an improvement on lipid profile among DPP-4I treated participants.

4.2.4. Effects on blood pressure

Participants in the current study recorded improvements overtime in systolic and diastolic blood pressures. However, no time*group interactions were found. The GLP-1RA participants had a higher systolic blood pressure reduction, compared to the other groups.

The existing scientific history shows that GLP-1RA in hypertensive patients with type 2 diabetes mellitus showed decreased systolic and pulse pressure, and an increase in heart rate [17], while in the case of DPP-4I there were controversial data on its antihypertensive effects, although they could decrease vascular stiffness and hypertension by improving endothelial function [18]. Phrommintikul et al. [22] found no significant changes in systolic and diastolic pressures in patients with vildagliptin (DPP-4I).

5. Strengths and limitations

The current study included many participants (n = 6165); however, the difference in the number of participants in the different groups, being the group of subjects treated with GLP-1RA (n = 49) and DPP-4I (n = 397), which collected the lowest number of participants is an issue itself, and may have influenced the results obtained.

It is important to note that the subjects included in the current study already established the pharmacological treatment for diabetes mellitus before the start of the study and, therefore, before starting the intervention with a healthy lifestyle; so, the environment in which the current study was carried out may differ from that of the published clinical trials. That itself is a limitation of the study. Moreover, this could also led to an indication bias, as practitioners freely provided the treatment, and some drugs could have been prescribed for difficult/easier cases or under special conditions as doctors willing to update. Changes in treatment dosage were not considered in the current study, which might be a limitation and should be furtherly studied. However, strength of the current study is that the subjects included in the different groups maintained the same treatment throughout the study period.

Food and tobacco consumption data were collected using the survey method, so an error arising from self-declaration may have been introduced. However, validated questionnaires for the study target population were used in the current study. In addition, subjects were previously trained and quality control was followed to minimize bias.

Finally, under ethical consideration, a limitation may be considered as comparison was made between treated patients with diabetes (3 groups) vs. untreated patients without diabetes instead of vs. untreated patients with diabetes, which obviously is out of ethical rules.

6. Conclusions

In patients with MetS and established and stable pharmacological treatment for diabetes, when a healthy lifestyle intervention was applied, those treated with GLP-1RA and DPP-4I obtained a better glycemic profile, but anthropometric improvements were modest. Further studies are needed on the long-term effects of these drugs on the healthy lifestyle setting and in the presence of Mets.

Institutional Review Board Statement

Research Ethics Committees from all recruitment centers approved the study protocol, according to the ethical standards of the Declaration of Helsinki. All participating centers have the ethics approval and consent from all the ethic committees, and within them it was approved by the Ethics Committee of the Balearic Islands (ref. IB 2251/14 PI). All participants were informed of the purpose and the implications of the study, and all provided the written informed consent to participate.

Informed Consent Statement

The results and writing of this manuscript followed the Committee on Publication Ethics (COPE) guidelines on how to deal with potential acts of misconduct, maintaining integrity of the research and its presentation following the rules of good scientific practice, the trust in the journal, the professionalism of scientific authorship, and the entire scientific endeavor. Written informed consent has been obtained from the patient(s) to publish this paper if applicable.

Western blots

No Western blots are included in this manuscript.

Clinical trials registration

The trial was registered at the International Standard Randomized Controlled Trial (ISRCTN: http:// www.isrctn.com/ISRCTN89898870) with number 89898870 and registration date of 24 July 2014, retrospectively registered.

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CRediT authorship contribution statement

RP, CB, and JAT provided literature searches and review and prepared the main outline of the manuscript and approved the final manuscript. All authors contributed substantially to the acquisition of data or analysis and interpretation of data. All authors revised the article critically for important intellectual content. All authors approved the final version to be published.

Conflict of interest statement

JS-S reports serving on the board of and receiving grant support through his institution from the International Nut and Dried Fruit Council, and Eroski Foundation. Reports serving in the Executive Committee of the Instituto Danone Spain and on the Scientific Committee of the Danone International Institute. He has received research support from Patrimonio Comunal Olivarero, Spain; and Borges S.A., Spain. Reports receiving consulting fees or travel expenses from Danone; Eroski Foundation, Instituto Danone - Spain, and Abbot Laboratories.

Data Availability

There are restrictions on the availability of data for the PREDIMED-Plus trial, due to the signed consent agreements around data sharing, which only allow access to external researchers for studies following the project purposes. Requestors wishing to access the PREDIMED-Plus trial data used in this study can make a request to the PREDIMED-Plus trial Steering Committee chair: jordi.salas@urv.cat. The request will then be passed to members of the PREDIMED-Plus Steering Committee for deliberation.

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Further reading

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