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Policaptil Gel Retard in adult subjects with the metabolic syndrome: Efficacy, safety, and tolerability compared to metformin☆

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ABSTRACT

Background: Policaptil Gel Retard® (PGR), is a new macromolecule complex based on polysaccharides slowing the rate of carbohydrate and fat absorption. It proved to significantly reduce body weight, acanthosis nigricans expression, HbA1c levels, and glucose metabolism abnormalities in obese, hyperinsulinemic adolescents. No such data are available for adults.
Aim: to compare the effects of PGR vs. metformin in adult subjects with the Metabolic Syndrome (MS) and T2DM on a Low Glycemic Index diet.
Subjects and methods: This spontaneous clinical, longitudinal, single-blind, randomized study based on a per-protocol analysis enrolled 100 outpatients with MS and T2DM consecutively referring to our clinic for three months, and randomly assigned to either the active treatment (**Group A**:, 6 tablets/day) or the comparator (**Group B**: Metformin tablets, 1500–2000 mg/day in two divided doses during the two main meals, to minimize side effects) to be taken 30 min before each main meal in equally divided doses. Serum lipid profile, anthropometry, HOMA-IR index, and tolerability parameters were evaluated before and after a 6-month follow-up period.
Results: all parameters improved at a similar rate in both groups but for the lipid profile, which got even better in Group A. Group A also experienced less prominent gastrointestinal side effects than its counterpart.
Conclusion: For the first time, we showed the non-inferiority of PGR compared to metformin in obese adult subjects with the MS and T2DM as for glycemic control and a clear-cut superiority of PGR in terms of both serum lipid-lowering capacity and tolerability.

Introduction

A cluster of risk factors for cardiovascular (CV) disease including high blood pressure, dyslipidemia (raised triglycerides and lowered high-density lipoprotein cholesterol), high fasting glucose, and central obesity, also known as the metabolic syndrome (MS) and type 2 diabetes mellitus (T2DM) are most often associated with each other within the same individual [1,2]. Various diagnostic criteria were proposed for the MS over time [3,4] until 2009 when a consensus document was published to harmonize them [4] by identifying the presence of obesity as the primary criterion (defined as abdominal circumference ≥95 cm in men and ≥80 cm in women), as well as at least 2 following criteria: (i) triglycerides ≥150 (mg/dL); (ii) HDL-Cholesterol <40 mg/dL in men, <50 mg/dL

Abbreviations: ERD, energy restricted diets; MS, Metabolic Syndrome; T2DM, type 2 diabetes; RCD, reduced carbohydrate diets; LGI, low glycaemic-index; PGR, Policaptil Gel Retard; BMI, Body Mass Index; eGFR, calculated glomerular filtration rate; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; CV-Risk, Cardio-Vascular risk; MET, Metabolic Equivalent of Task.

☆ **Clinical Trial Registration** from Ethical Committee of Vanvitelli University: Protocol n.1287, June 23, 2019.

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in women or being on statin treatment; (iii) systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or being on antihypertensive therapy; (iv) fasting blood glucose ≥100 mg/dL. Indeed, all those parameters are directly or indirectly linked to insulin resistance or associated with T2DM [5–7]. In any case, the presence of T2DM further increases the already high cardiovascular risk (CVR) observed in patients with the MS [8,9]. An estimated 463 million adults aged 20–79 years are currently living with diabetes, representing 9.3% of the world's population in this age group (IDF), and Obesity and diabetes have reached epidemic proportions [10,11]. Managing obesity efficiently can delay the progression from prediabetes to T2DM [12,13] and may also prove beneficial in T2DM treatment [14–19]. According to previous small studies, a severely energy-restricted diet (ERD) can reduce glycated hemoglobin (HbA1C) to <6.5% (48 mmol/mol) and fasting plasma glucose (FPG) to <126 mg/dL (7.0 mmol/L) in the absence of any pharmacological treatment in obese patients with T2DM and MS [18–21]. As satiety is inversely related to glucose levels, and related insulin sensitivity may better promote long-term weight loss by decreasing hunger [22], dietary recommendations are central components of any comprehensive weight-loss program, and ERDs represent the conventional treatment for obesity, T2DM and metabolic syndrome (MS). Nevertheless, according to current literature and our own experience, they are not easy to follow, and the weight loss finally achieved through great efforts is hardly maintained long enough.

Policaptil Gel Retard® (PGR) is a macromolecule complex covered by a European patent (no. 1679009) and based on polysaccharides slowing the rate of carbohydrate and fat absorption. It is derived from high-fiber raw materials including glucomannan (*Amorphophallus konjac*) [23,24], cellulose, *Opuntia* pulp stem (*Opuntia ficus indica*) [25], chicory root (*Cichorium intybus*) [26,27], freeze-dried mallow root mucilage (*Althaea officinalis*) [28], freeze-dried flaxseed mucilage (*Linum usitatissimum*) [29] and freeze-dried linden flower mucilage (*Tilia platyphyllos Scop*) [30]. Recent studies on obese, hyper-insulinemic adolescents indicate that, when used in conjunction with a low glycemic index (LGI) diet, PGR significantly reduces acanthosis nigricans expression, HbA1c levels, and glucose metabolism abnormalities, such as impaired glucose tolerance (IGT) and T2DM [30]. The effect of PGR seems to be related to a reduction in the post-meal blood glucose and insulin peaks [31,32]. As glucose absorption directly regulates pancreatic insulin release, the attenuated insulin response was likely due to slow glucose absorption [31]. Another study compared the effect of off-label Metformin - the most used, first-step, oral medication against T2DM [33,34], also reducing lipid absorption by the gastrointestinal tract [32] - vs. Metformin + PGR administration in children and adolescents with the MS [36]. According to its results, add-on PGR significantly reduced BMI, HbA1c, and HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) vs. controls, and increased insulinogenic and disposition indices (Matsuda Index), respectively, even more than already observed with metformin alone [35]. Recent studies also indicate a significant effect of PGR on intestinal microbiota [36].

Despite such interesting metabolic effects in children and teenagers, PGR still awaits evaluation in adults with similar metabolic disorders. The purpose of our study was to compare PGR's to metformin's effects in adult subjects with MS and T2DM kept on an LGI diet.

Subjects and methods

This spontaneous, longitudinal, single-blind, randomized, clinical study, based on a per-protocol analysis, enrolled 100 outpatients with MS and T2DM meeting the enrollment criteria, consecutively referred to our clinic during three months (Fig. 1). They were randomly assigned to either the active treatment, taken 30 min before the main meals (Group A: PGR, as six 725 mg tablets providing 4350 mg/day and equally divided between 3 meals), or the comparator (Group B: Metformin tablets, 1500–2000 mg/day, equally divided between the two main meals to minimize side effects).

The study was conducted under the 1975 Helsinki Declaration and subsequent amendments and was formally approved by the Ethics Committee of the University of Campania "Luigi Vanvitelli" (Protocol n.1287, June 23, 2019). All participants signed informed consent and data were processed anonymously according to good clinical practice guidelines.

Inclusion criteria

- metabolic syndrome (defined according to the consensus document 2009) (4)
- age between 18 and 70 years,
- body mass index (BMI)> 30 kg/m^2,
- altered glucose profile (FPG ≥ 126 mg/dl - HbA1c ≥ 42 mmol/mol), or overt T2DM, known for no more than 1 year (±0.5) (ADA criteria 2019)
- altered lipid profile (Total Cholesterol ≥ 200mg/dl, LDL-Cholesterol ≥ 100 mg/dl),
- reliability (being frequently visiting the clinic)
- acceptance of informed consent
- normal estimated glomerular filtration rate (eGFR) [60–90 ml/min/1.73 m2]
- no micro-macro-albuminuria
- no previous drug intervention against metabolic disorders.

Exclusion criteria

- insulin treatment,
- previous bariatric surgery interventions,
- pregnancy or breastfeeding,
- disabling conditions, serious liver, kidney or neoplastic diseases, dementia and/or inability to regularly comply with prescriptions,
- known hypersensitivity/intolerance to treatment/history of drug allergy or known allergic disease
- irritable bowel disease or dyspepsia.

Low glycemic-index hypocaloric diet: during the study, all patients received a low-calorie diet (20–25% less than the number of calories required to maintain current weight) varying in percentages of proteins (10–20%), fat (20–30%, saturated ones being less than 10%), and carbohydrates (50–60%, sucrose being less than 5%). Dietary regimens were prepared by a dietician expert of overweight/obese people with T2DM to meet each individual patient's wish, tastes and needs.

Treatment Adherence and side effects: All subjects completed a daily logbook by recording food changes regarding prescriptions and the number of daily tablets to let adherence be verified and any side effects throughout the whole treatment period. Diet-adherence allowed checking the rate of nutritional advice breaches in terms of excess carbohydrates and calories.

Adhesion was verified through a weekly log: completing at least five days per week was considered acceptable. The side effect logbook section consisted of ten dichotomic questions (answers being yes/not) concerning gastrointestinal disorders. The above-mentioned diary had been previously tested for validity and reliability in a sample of 10 health care workers by verifying the concordance of the answers given three times in two weeks by the

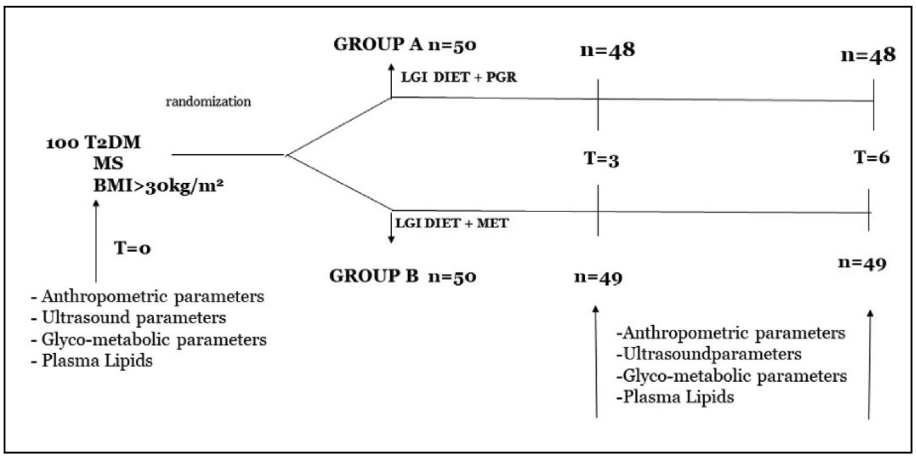

Fig. 1. Study design. *PGR = Policaptil Gel Retard®, MET = Metformin.*

same subject (mean concordance degree being 95 ± 5%) as previously described [37].

To allow non-utilized drug residues calculation for treatment adherence evaluation, at each follow-up step, participants also took notes of any drug packs taken.

Patients were encouraged to do aerobic daily physical activity, such as a walk, for a minimum of 3 Met (Metabolic Equivalent of Task) and take records of that regularly in the diary. 16 subjects from the treatment group and 14 from the control group were smokers (13 ± 4 cigarettes/day and 10 ± 5/day, respectively).

During follow-up, all patients received weekly motivational phone support on diet, physical activity, and treatment adherence.

The main clinical features of enrolled patients are shown in Table 1.

Parameters under study included: (i) anthropometry: body mass index (BMI), waist circumference (WC) and visceral fat percentage (% VF); (ii) blood chemistry: HbA1c and HOMA-IR (homeostatic model assessment for insulin resistance), and C-Peptide; Triglycerides, Total cholesterol, LDL- cholesterol, AST, ALT, gamma-GT and alkaline phosphatase (Automatic biochemistry analyzer with integrated system Selecta Pro XI, [Elithech, USA]. and commercially available ELISA kit, as appropriate); (iii) adherence to treatment + count of pills found in the drug packs used during each study period; (iv) side effects; (v) adverse effects: clinical history + circulating AST, ALT, gamma-GT, alkaline phosphatase, blood creatinine levels.

HOMA-IR vas calculated by replacing insulin with fasting C-peptide in modified homeostasis model assessment to evaluate

Table 1
Baseline clinically relevant participants' parameters. As shown, no significant differences were apparent between the two groups. Absolute, percent, or M ± SD values were reported, as appropriate.

	Group A PGR	Group B Metformin	*p*
Subjects (n.)	50	50	–
Male (n.)	26	27	n.s.
Age (year)	63 ± 7	64 ± 6	n.s.
Waist circumference (cm)	114 ± 10	115 ± 9	n.s.
BMI (kg/m^2)	35 ± 4	36 ± 5	n.s.
GV (%)	23.0 ± 6	24.0 ± 6	n.s.
Systolic BP (mmHg)	138.3 ± 14.4	137.9 ± 13.6	n.s.
Diastolic BP (mmHg)	82.7 ± 8.2	81.5 ± 8.4	n.s.
Heart rate (beats/min)	73.0 ± 7.6	72.8 ± 9.3	n.s.
Fasting plasma glucose (mg/dl)	197 ± 9.0	193 ± 8.8	n.s.
HbA1c (%)	7.6 ± 0.9	7.5 ± 0.9	n.s.
HOMA-IR	4.8 ± 0.8	4.7 ± 0.7	n.s.
Peptide-C	1.6 ± 0.5	1.6 ± 0.5	n.s.
Total cholesterol (mg/dl)	234 ± 16	230 ± 18	n.s.
HDL cholesterol (mg/dl)	41 ± 4	41 ± 3	n.s.
LDL cholesterol (mg/dl)	159 ± 14	151 ± 18	n.s.
Triglycerides (mg/dl)	198 ± 23	198 ± 21	n.s.
AST (UI/L)	29 ± 9	29 ± 8	n.s.
ALT (UI/L)	29 ± 8	27 ± 9	n.s.
γGT (UI/L)	21 ± 7	24 ± 5	n.s.
Uric Acid (mg/dl)	7.3 ± 1.8	7.5 ± 1.7	n.s.
Cardio-vascular risk factors (% of subjects)			
Subjects meeting diagnostic criteria for metabolic syndrome (%)	100	100	–
Waist circumference exceeding reference range (%)	65	61	n.s.
Current smokers (%)	15	16	n.s.
Low HDL cholesterol levels (%)	60	62	n.s.
Family history of premature heart disease (%)	10	11	n.s.
Hypertension (%)	58	55	n.s.
>2 Risk Factors (%)	79	80	n.s.

insulin resistance and islet beta-cell function [Homa-IR (CP) = 1.5 + fasting blood glucose x fasting C-peptide/2800 (F = 5. 511, P = 0.029)] [38].

All parameters were measured at baseline (T-0) and after 3 (T-3) and 6 months (T-6), respectively.

Visceral fat was measured with Body Metrix BX2000, Intela-Metrix, Inc. Brentwood CA, US), a validated instrument based on ultrasound technology, allowing direct and immediate subcutaneous fat thickness measurement to avoid annoying and operator-dependent manual plication maneuvers [39].

Statistical analysis

Sample size: based on the primary endpoint, by considering a drop-out <20%, the estimated sample size granting a 90% power and an alpha error of 0.02 was 100 subjects. A $p < 0.05$ was chosen as the least acceptable level of statistical significance. All assessments were made using the SPSS/PC software (IBM SPSS Statistics version 18.2).

The results were expressed as average ± SD or % of the total number of patients completing the study. The number of drop-outs - consisting of two patients from group A and one from group B stopping for personal reasons, not because of side effects - was irrelevant as for statistical evaluation. Observed differences were evaluated according to the analysis of variance for repeated measures (rANOVA) supplemented by a two-tailed Student's t-test for parametric variables and by the Mann-Whitney *U*test with 95% confidence intervals (CI) for nonparametric variables. The chi-square test with Yates correction or Fisher Exact test was used to compare categorical variables.

Results

48 subjects from Group A and 49 from Group B completed follow-up (Fig. 1 and Table 1). Adherence to physical activity and diet was very high in all patients, and in greater detail, patients adhered to 95% of nutritional prescriptions on 91% treatment days, without substantial differences between the two groups.

Reported side effects were mild and quite similar across groups. In greater detail, the following were recorded in **Group A** vs **Group B**, respectively: drowsiness (n = 1 vs. n = 1), acid regurgitation (n = 2 vs. n = 2), post-prandial nausea/vomiting (n = 1 vs. n = 1), itching (n = 1 vs. n = 1), headache (n = 1 vs. n = 3), dizziness and/or fainting (n = 1 vs. n = 1), cold sweat with/without hunger pangs (n = 2 vs. n = 3), palpitations (n = 2 vs. n = 3), tachycardia (n = 1 vs. n = 1). **Group B** experienced gastro-intestinal side effects more frequently, though: meteorism (n = 3 vs. n = 19; $p < 0.05$), flatulence (n = 5 vs. n = 21; $p < 0.05$), diarrhea (n = 0 vs. n = 5; $p < 0.05$), long and tiring digestion (n = 1 vs. n = 7; $p < 0.05$). No people experienced constipation. In most cases side effects tended to resolve spontaneously during treatment. Slight percent variations in biochemical safety parameters during the study period were similar in the two groups, ranging 0.2–0.5%.

In general, based on the absence of any significant differences between groups at baseline and during follow-up, PGR treatment results were similar to those observed with metformin. From Table 2, a progressive decrease in BMI, WC, and VF% is clearly apparent compared to baseline and gets significant at six months. ($p < 0.01348$ T-6, $p < 0.01661$, $p < 0.01979$ vs baseline, respectively).

Surprisingly, PGR and metformin effects on glucose metabolism consisted of a comparable, significant reduction in HbA1c, C-peptide, FPG, and HOMA-IR vs baseline (see Table 3).

As shown in Table 4, PGR and Metformin were associated with a significant progressive decrease of all serum lipid parameters, with a more pronounced effect for PGR (Fig. 2**).**

Discussion

The exceptionally high adherence rate to treatment, physical activity, and diet in all patients surprised us. It most likely depended on the fact that participants appreciated very much nutritional treatment personalization and the close follow-up, consisting of regular phone calls including weekly educational message reinforcement.

For the first time, study results documented a comparable efficacy of Policaptil Gel Retard and metformin in adult people with MS and T2DM in terms of improved FPG (A = T-0:197 ± 9.0 vs T-6: 117.5 ± 10.3, $p < 0.01$ and B = T-0: 193.6 ± 8.8 vs T-6: 121 ± 12.7; $p < 0.01$, respectively), HbA1c (mmol/mol) (A = T-0: 60 ± 15 vs T-6: 50 ± 14, $p < 0.036$; and B = T-0: 58 ± 14 vs T-6 = 50 ± 16; $p < 0.029$, respectively), and the HOMA-IR index of insulin resistance (A = T-0: 4.8 ± 0.8 vs T-6 = 2.6 ± 0.5; $p < 0.01$, and B = T-0: 4.7 ± 0.7 vs T-6: 2.5 ± 0.5; $p < 0.01$, respectively).

Similarly, both treatments, in association with LGI diet, induced a significant, comparable reduction in BMI (kg/m^2) (A = T-0: 35 ± 4 vs T-6: 29 ± 3; $p < 0.01$, and B = T-0: 36 ± 5 vs T-6: 30 ± 3, $p < 0.01$, respectively), WC (cm) (A = T-0: 114 ± 10 vs T-6 = 86 ± 5, $p < 0.01$, and B = T-0: 115 ± 9 vs T-6 = 88 ± 5, $p < 0.01$, respectively) and VF% (A = T-0: 23 ± 6 vs T-6: 15 ± 4 $p < 0.01$ and B = T-0: 24 ± 6 vs T-6: 14 ± 4, $p < 0.01$, respectively), with both redistribution and reduction of accumulated fat as early three months, and even more six months after treatment initiation.

Conversely, the response of the lipid parameters was different for the two treatments at T-6. In fact, while the effect of metformin + diet was modest, the improving effect of PGR + diet was significantly more pronounced already at three months and even more at six months, when lipid parameters got significantly lower also between groups, as follows: Total Cholesterol (mg/dl) (A t0 = 234 ± 16 – t6 = 175 ± 17) vs (B t0 = 230 ± 18 – t6 = 198 ± 16), LDL-cholesterol (mg/dl) (A t0 = 159 ± 14 – t6 = 106 ± 14) vs (B t0 = 151 ± 18 – t6 = 135 ± 14) and triglycerides (mg/dl) (A t0 = 198 ± 21 – t6 = 156 ± 15) vs (B t0 = 198 ± 23 – t6 = 172 ± 12).

It is undeniable that the low-calorie. low-glycemic index diet had an essential role in improving all the parameters under study, inducing lower FPG and HbA1c levels and a powerful stimulus to reduce body fat, thus supporting literature data. The presence of

Table 2

Anthropometric parameters: *comparison of body mass index (BMI), waist circumference (WC), and visceral fat (% VF) at baseline (T-0), after 3 (T-3) and* 6 months *(T-6), respectively between groups A (PGR and LGI diet), and B (Metformin and LGI diet). **p<0.01 vs. T-0; *p<0.05 vs. T-0; $ p<0.05 vs. T-3.*

Anthropometric parameters					Ultrasound Parameters	
	BMI (Kg/m^2)		WC (cm)		VF (%)	
Group	A	B	A	B	A	B
T-0	35 ± 4	36 ± 5	114 ± 10	115 ± 9	23 ± 6	24 ± 6
T-3	33 ± 2	33 ± 4	95 ± 4**	96 ± 4**	19 ± 4*	19 ± 6*
T-6	29 ± 3**	30 ± 3**	86 ± 5**$	88 ± 5**$	15 ± 4**$	14 ± 4**$

Table 3
Glyco-metabolic parameters: *comparison of HbA1c (%), fasting C-peptide and glucose levels, and HOMA-IR at baseline (T-0), after 3 (T-3) and* 6 months *(T-6), respectively, in groups A (PGR + LGI diet), and B (Metformin + LGI diet). Statistical significance: **p<0.01 vs. T-0; *p<0.05 v.s T-0; $ p<0.05 vs. T-3 or vs T-0.*

Glyco-metabolic parameters								
	HbA1c (mmol/mol)		Fasting C-peptide (μg/L)		Fasting plasma glucose (mg/dl)		HOMA-IR	
Group	A	B	A	B	A	B	A	B
T-0	60 ± 15	58 ± 14	1.6 ± 0.5	1.6 ± 0.5	197 ± 9.0	193.6 ± 8.8	4.8 ± 0.8	4.7 ± 0.7
T-3	55 ± 14	55 ± 16	1.4 ± 0.5	1.4 ± 0.5	143 ± 11.2$	140.9 ± 10.7$	3.3 ± 0.8$	3.3 ± 0.8$
T-6	50 ± 14	50 ± 16	1.0 ± 15*	1.0 ± 0.5*	117.5 ± 10.3**$	121 ± 12.7**$	2.6 ± 0.5**$	2.5 ± 0.5**$

Table 4
Compared serum lipid parameter changes as observed in the two groups at baseline (T-0) and at the two follow-up steps (T-3, and T-6). Statistical significance of comparisons: (i) within group: T-6 vs. T-0: **p < 0.01; *p < 0.05; T-6 vs. T-3: $ p < 0.05; T-3 vs. T-0: & <0.05; (ii) between group: A vs B: ° p < 0.05

Serum Lipids						
	Total Cholesterol (mg/dl)		LDL- Cholesterol (mg/dl)		Triglycerides (mg/dl)	
Group	**A**	**B**	**A**	**B**	**A**	**B**
T-0	234 ± 16	230 ± 18	159 ± 14	151 ± 18	198 ± 21	198 ± 23
T-3	201 ± 14&	221 ± 14	127 ± 12&	138 ± 12	165 ± 14&	176 ± 16
T-6	175 ± 17**$	198 ± 16*°	106 ± 14**$	135 ± 14*$°	156 ± 15**	172 ± 12*°

fiber and low glycemic index foods, though, resulted in a reduced stimulus to insulin secretion, as documented by the reduction of the peptide-C values (μg/l) (A = T-0: 1,6 ± 0,5 vs. T-6: 1,0 ± 1,5, p < 0.05, and B = T-0: 1,6 ± 0,5 vs. T-6: 1,0 ± 0,5, p < 0.05, respectively), which is produced by the pancreas in equimolar quantities as insulin.

As the diet treatment was present in both groups, we must infer that the two treatments' contribution was quite similar, although achieved differently. The mechanisms underlying metformin effects are complex and not fully elucidated. Besides enhancing glucose uptake through the expression of muscle GLUT4 receptors, metformin reduces hepatic gluconeogenesis and glycogenolysis - processes through which hepatic glucose production increases. It also promotes fatty acid oxidation and decreases the synthesis of lipoproteins and NEFA (non-esterified fatty acids), partially responsible for the insulin resistance observed in patients with MS or T2DM [40–43].

Based on the study results, PGR is equally improving body weight, diabetes-related parameters, and insulin resistance as metformin. It also better affects lipid parameters. However, the two treatments' tolerability was substantially different due to the presence of a two to three times higher percentage of patients on metformin suffering from gastrointestinal disorders compared to their counterparts. Ours is the first comparative data on PGR and Metformin's metabolic effects in adults with MS and severely insulin-resistant T2DM, as favorable PGR effects were only referred to obese adults with T2DM [30–33] and in a pediatric population [34].

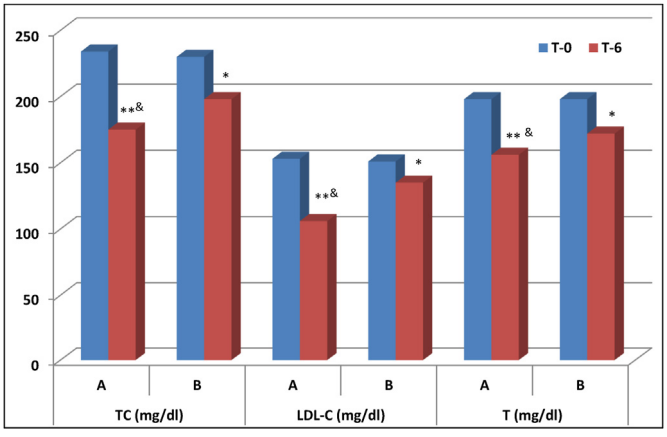

Fig. 2. Significance of within- and between-group differences (i.e., T-0 [baseline] vs. T-6 [end of treatment], and A group [PGR] vs. B group [metformin], respectively). T-6 vs. T-0: **p < 0.01; *p < 0.05; Group A vs. Group B: & p < 0.05.

Although those disorders were transient, probably based on the fact that we enrolled patients free of irritable bowel disease, things are expected to be quite different in real life [44,45]. In fact, (i) patients often do not have a chance to inform the doctor of the problems they can encounter promptly; (ii) adherence to pharmacological treatment is inversely proportional to the presence and extent of side effects; (iii) appropriate selection of patients to be prescribed metformin is not so frequent because all guidelines intend the drug as the first level treatment option for people with T2DM. Adherence to metformin-based treatment regimens for T2DM is currently suboptimal due to a complex array of patient-, treatment- and doctor-related barriers, including gastrointestinal disturbances and physical or psychological swallowing troubles associated with large tablets [44,45] (often underestimated by physicians). Patients usually refrain from discussing these issues with their primary care providers for fear of being misunderstood, so that, in some cases, delays in addressing them lead to reduced glycemic control [45].

Moreover, we underlie the significantly more noticeable reduction of LDL-Cholesterol associates with PGR than with the comparator (33.3% vs. 10.3%, respectively) observed in subjects with MS and T2DM, known to be burdened with severe cardiovascular risk. The importance of such a finding relies on the fact that diet alone can reduce total cholesterol by no more than 20%. Indeed, only nutritional regimens allowing for a total fat intake of 7% (like the so-called Ornish diet), which are known to be challenging to adhere to for an extended period, can perform better [46,47].

Limitations

We cannot compare other authors' results to ours because this is the first paper comparing PGR to metformin in adults with MS and severely insulin-resistant T2DM. Moreover, due to our sample population's small size and the limited time-frame of our study,

further investigations are needed involving a larger sample and a more extended observation period to further validate our preliminary results.

In conclusion, we can say that, when taken 30 min before the two main meals, 4350 mg PGR/day: (i) are not inferior to 1500–2000 mg metformin/day, (ii) are more effective on lipid parameters, and (iii) are better tolerated. Therefore, PGR utilization may turn out to be a valid therapeutic alternative in obese patients with MS and T2DM.

Strengths

For the first time, we showed the non-inferiority of PGR compared to metformin in obese adult subjects with MS and T2DM for glycemic control, and even a clear-cut superiority of PGR in terms of both serum lipid-lowering capacity and tolerability.

Funding

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for works integrity as a whole, and have given their approval for this version to be published.

Author contributions

GG has devised the protocol, TDC and SG, and FS critically revised and approved the paper. All complied with data collection, critically assessed the results, and approved the final text.

Compliance with ethics guidelines

This study was conducted in conformance with good clinical practice standards. The study was led in accordance with the Declaration of Helsinki 1975, and subsequent amendments. Written informed consent was obtained from all participants before enrollment.

Data availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of competing interest

Sandro Gentile, Giuseppina Guarino, Teresa Della Corte, and Felice Strollo have no financial interests to declare concerning the present study nor received emoluments in any form.

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APPENDIX

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