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Probiotics In Incretin-Based Therapy for Patient Living with Obesity: A Synergistic Approach

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Abstract

Obesity is a multifactorial chronic relapsing disease correlated with various diseases and conditions, particularly metabolic syndrome, cardiovascular diseases, type 2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis. The incidence of these diseases is increasing with a global dimension affecting millions of people. One promising therapeutic approach for addressing obesity involves GLP-1 receptor agonists (GLP-1RAs). These drugs, such as liraglutide, mimic the action of the incretin hormone GLP-1, which promotes insulin secretion, slows gastric emptying, and reduces appetite. Clinical trials have shown positive results but with several side effects, reducing the adherence to therapy and the positive effects for patients. In this study we evaluate the synergistic effects of a low dose liraglutide therapy in association with an orally applied multispecies probiotics, developed to target metabolic disease. Our results show comparable results on metabolic parameters of the low dose liraglutide therapy in combination with a multispecies probiotic compared to published high dose data, yet accompanied by a significant reduction of adverse events and according to that a consequent major adherence to the therapy.

Keywords: Obesity, Incretin therapy, probiotics, emerging treatment, synergy

Introduction

Several studies highlight the crucial role of the gut microbiome, the community of bacteria, viruses, fungi, and archaea within its environment, capable of interacting with the internal and external environment, in maintaining homeostatic control of human health. The microbial colonization is associated to the development of metabolic diseases such as overweight, obesity, type 2 diabetes, metabolic syndrome, and hepatic steatosis [1]. A balanced intestinal microbiome, or eubiosis, is involved in various metabolic processes like vitamin production, bile acid transformation and secondary bile acid production, digestion, and nutrient absorption. Further, the intestinal microbiome is known to be crucial in various protection mechanisms such as development and maintenance of the gastro-intestinal barrier, tolerance toward food antigens, competition against pathogenic microorganisms [2, 3] and structuring of intestinal immune processes [4, 5]. Daily lifestyle habits, characterized by a disordered diet, low in fiber and high in fat (so called Western-style diet), associated with the use of drugs (antibiotics, proton pump inhibitors etc..), may contribute to an alteration of this delicate microenvironment (dysbiosis), facilitating the development of metabolic diseases and inflammation [6-11]. Although the role of the gut microbiome

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on overweight and obesity is still under investigation, several large cohort studies demonstrated the association of obesity with an intestinal dysbiosis, that is characterized by an alteration of the quantity and biodiversity of the intestinal microbiota. In particular, a shift in the ratio of Firmicutes (increased) to Bacteroidetes (decreased) [12-19] associated with an increase in Proteobacteria phylum (Gram-negative) [17] has been associated with obesity compared to normal-weight individuals. This bacterial flora imbalance on one side leads to an increase of the intestinal permeability (leaky gut) and production of endogenous lipopolysaccharide (LPS) [20-22] and its translocation to the blood circulation. Such alterations are responsible for the development of low-grade inflammation and insulin resistance, and on the other side select bacteria with a greater capacity of energy extraction from food [19], promoting the distribution of fat at abdominal-visceral level and increasing the risks for the developing of cardio-metabolic diseases. For the sustainable treatment of type 2 diabetes and obesity, intervention with multispecies probiotics has already been successfully tested in clinical trials. Recent studies highlighted how the use of a multispecies probiotic has produced both favorable results on glucose metabolism and HOMA-IR, as well as in the marked reduction of plasma levels of lipopolysaccharide (LPS), PCR, TNF-alpha, and an increase of adiponectin, suggesting a clear improvement in gut barrier function [23-26]. The results of these studies show an effect of probiotics on the management of overweight and diabetes and suggest that probiotics are a promising agent as adjuvant tool in the management of metabolic diseases.

Antidiabetic drugs can modulate the gut microbiota [27, 28], especially incretin drugs. Incretin drug therapy (INtestinal seCRETion of INsulin) has introduced unquestionable advantages in obesity management and reduction of obesity-related comorbidities [29]. Liraglutide, a glucagon-like peptide 1 receptor agonist (GLP-1RA) used in both diabetes and obesity management, is able to modulate insulin release through several mechanisms, resulting in a favorable effect on blood glucose, glycated hemoglobin, blood pressure, and lipid profile [30, 31]. However, in addition to its incretin effect, GLP-1RA is also able to induce a reduction in gastrointestinal transit, which, while having a positive effect in promoting satiety and slowing nutrient absorption, also promotes the proliferation of bacteria that contribute to gut dysbiosis, already present in patient with obesity [32], and which facilitate the onset of dose-dependent gastrointestinal side effects [33] (Table 1).

Finally, it has been observed that the combination of probiotics with metformin, resulted even in an improvement in metabolism with a simultaneous reduction in gastro-intestinal side effects [35]. On the basis of this scientific evidence and their pathophysiological relevance, we

Table1: GLP-1RA side effects and mechanisms based on the summary product characteristics of all registered GLP-1RA [34]. *Predominantly observed in combination with sulfonylurea agents, not with metformin. +++, very common (>1/10); ++, common (>1/100); +, uncommon (>1/1000); +/−, rare to very rare (>1/10 000).

Side effect	Intensity	Potential mechanism
Nausea	+++	Gastric emptying ↓, nausea centers activation
Vomit	++	Gastric emptying ↓, nausea centers activation
Diarrea	+++	Unknown
Constipation	++	Intestinal motility ↓
Flatulence	++	Unknown
Gastric reflux	++	Unknown
Pancreatitis	+/-	Unknown
Cholelithiasis	+/-	Weight loss, bile acids production ↓, gallbladder motility ↓
Hypoglycemia*	+/++	Insulin secretion ↑,
		Glucose absorption ↓
Rhinopharyngitis	+	Unknown
Anaphylaxis	+/-	Immunoreactive
Prerenal kidney failure	+/-	Vomiting dehydration, diuresis ↑

studied and applied an obesity protocol that involves the administration of a multispecies probiotic formulation in combination with a low-dose of liraglutide, in order to verify a possible therapeutic synergy able to achieve a therapeutic effect but with less gastro-intestinal adverse events and consequently better adherence to pharmacological therapy and rehabilitation pathway. In this study, we aimed to show the synergistic effect of a multispecies probiotic and liraglutide for the management of metabolic syndrome.

Methods and Material

Study Participants, study medication and Morphogram® software tool

This is a retrospective, 3-months weight loss intervention study with two arms (group A and group B) of patients with obesity (BMI ≥30). Group A (control), consisted of 27 patients (11 male and 16 female, mean age of 50 ± 16), followed a balanced normoproteic personalized diet (-500 kcal), meanwhile group B, consisted of 25 patients (4 male and 21 female, mean age 46.68 ± 28), followed the same diet as group A with the addition of Liraglutide at increasing dosage (Saxenda® applied via FlexPen device, Novo Nordisk) and the indication specific, multispecies probiotic OMNi-BiOTiC® METAtox (containing 2.5 x 10^9 cfu/g, *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Bifidobacterium lactis* W51, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56,

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Lactobacillus salivarius W24, *Lactococcus lactis* W19, *Lactococcus lactis* W58 per sachet in a matrix of corn starch, maltodextrin, potassium chloride, hydrolyzed rice protein, magnesium sulfate, enzymes -amylases- and manganese sulfate).

Liraglutide initial dose was 0.6 mg/day for 10 days (in men and in women) and increased of 0.6 mg/day every 10 days until reaching the dosage of 1.2 mg/day in women and 1.8 mg/day in men, while 3g of the multispecies probiotic was taken once a day before breakfast for the whole intervention period of 3 months. Every patient had a 3 months follow-up period with usually a monthly medical examination, to evaluate the individual health risk. At each timepoint the following parameters were measured, with anthropometric standard [36]: Height (only at baseline), weight, arm circumference, forearm circumference, wrist circumference, neck circumference, waist circumference, abdominal circumference, hip circumference and thigh circumference.

For accurate health status monitoring, staging of individual risk for the development of cardio metabolic diseases, and to overcome the limitations of the classical parameters currently used (BMI, Weight and Waist Circumference), we employed several anthropometric ratios that can assess the conservation or loss of lean mass. These parameters are waist-to-height ratio (WHtR), waist-to-hip ratio (WHR), waist-to-thigh ratio (WTR) and "excessive abdominal volume" (AV+). In detail, the WHtR is a parameter that can personalize the risk of cardiovascular disease according to individual constitution; indeed, with the same waist circumference, the risk increases with lower height [37-39]. The waist-to-hip ratio (WHR) is an indicator of gynoid or android distribution of body fat. The WHR correlates with cardiovascular events or protection against them [40]. Furthermore, there is evidence that a large hip circumference is an indicator of greater deposition of subcutaneous fat not only in the hips, but also in the abdomen. Therefore, for a given Waist Circumference (WC), individuals with a larger hip circumference have less visceral fat and may have additional advantages for gaining gluteal and leg muscles [41-43]. The waist-to-thigh ratio (WTR) is an important and fundamental indicator of diabetic/sarcopenic risk because it closely tracks central adiposity and its relationship with lean body mass. Therefore, WTR allows the early identification of the trend towards sarcopenic obesity. In fact, as the waist circumference increases and the median circumference of the thigh decreases, the functionality of the lean body mass is compromised, glucose tolerance is reduced, insulin resistance increases [37], and diabetes can appear [44–46]. Therefore, an increasing WTR value indicates a worsening of the metabolic status, which occurs when the relation between waist and thigh circumferences is unbalanced in favor of adiposity, whereas the reduction of the WTR denotes an improvement [41, 42].

Excessive Abdominal Volume (AV+) is a new parameter introduced by the Morphogram® software (Nubentech Srl), which is very sensitive in monitoring changes in individual excessive abdominal volume. It uses the AVI formula which measures the abdominal volume (in liters) of the truncated cone delimited by the abdominal circumference, measured at the level of the iliac spines (denoting the widest points of the abdomen) and hip circumference, measured as the longest circumference at the buttocks (denoting the widest width of the pelvis). It has been reported that the concordance of the evaluation of waist circumference and abdominal volume index (AVI) represents a highly significant indicator of metabolic syndrome and diabetic risk [47-49]. The AV+ is obtained by subtracting from the AVI measured in the patient, the AVI that patient should have had if he or she had an abdominal circumference equivalent to half of his/her height (i.e, with no risk of cardiovascular or metabolic diseases), and proportional hip circumference.

Questionnaire

Finally, a questionnaire to assess adverse gastro-intestinal effects and also to identify underlying undiagnosed eating disorder, was administered at the first follow-up visit after one month (figure 1). Patients with pre-existing gastro-intestinal symptoms, with multiple drug therapy, and with binge eating, were excluded from the study. In order to obtain a statistically significant number of patients for the questionnaire and to get more comparable results with data reported in literature, we included the side effect questionnaires of 81 patients who filled out the questionnaire at the first follow-up visit, but who did not yet complete the 3 months therapy. Clinical parameters were collected from 27 (group A) and 25 (group B) patients.

Statistical Analysis

All data collected were analyzed with anthropometric software Morphogram® (Nubentech Srl) and compared both between the two groups and with available published data on liraglutide effects at 3 mg/day dosage [50]. All reported data were analyzed with a 2 tailed sample T-test.

Results

After 3 months of therapy, both groups showed a reduction in weight, BMI, and anthropometric index of WC, AV+, WHtR, while there was no significant reduction in WTR. Comparison between groups showed that patients that underwent the diet in combination with the GLP-1RA and OMNi-BiOTiC® METAtox had a greater and significant reduction on all parameters compared to the control group, highlighting a major selective central adiposity loss (AV+ reduction), alongside with a reduction in cardio-vascular risks (WC and WHtR reduction) while preserving lean mass (stable WTR) (table 2, figure 2).

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GLP-1 AND DUAL AGONIST ADVERSE EFFECTS QUESTIONNAIRE

Nutritional specialistic center
Regional reference center for the Italian Obesity Society (SIO)
Director: Dr. Prof. Paolo De Cristofaro
c/o SANI MEDICAL CENTER, Castellalto (TE)

1. I'M TAKING : ☐ SEMAGLUTIDE, ☐ TIRZEPATIDE, ☐ LIRAGLUTIDE, FOR N.___MONTH/S
2. ☐ I FOLLOWED A PROBIOTIC TREATMENT PRELIMINARY TO THE PRESENT THERAPY.
3. ☐ I'M TAKING A PROBIOTIC TREATMENT DURING THE PRESENT THERAPY.
4. ☐ I'M TAKING OTHER MEDICATIONS ALONGSIDE THIS THERAPY.
5. ☐ I HAVE A PERSONAL PREDISPOSITION TO DIGESTIVE DISORDERS (GASTRITIS, SLOW DIGESTION, METEORISM, REFLUX, INFLAMMATORY BOWEL DISEASE ETC..)
6. ☐ **NO, I DIDN'T HAVE ADVERSE EFFECTS** → **(IF YOU ANSWERED "NO", STOP HERE)**

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7. ☐ **YES, I HAD ADVERSE EFFECTS** → **(IF YOU ANSWERED "YES", GO ON)**
8. WHEN ADVERSE EVENTS OCCURRED ?

A. ☐ SINCE FIRST ADMINISTRATION
B. ☐ AFTER FEW DAYS
C. ☐ AT DOSAGE RISE (DOSAGE AT WITCH THE ADVERSE EFFECT OCCURRED_____)

9. HOW LONG THE ADVERSE EFFECT LASTED? :

A. ☐ ONE DAY
B. ☐ FEW DAYS
C. ☐ SEVERAL DAYS

10. SPECIFY THE MOST RELEVANT SYMPTOMS AND THE INTENSITY, ACCORDING TO A SCALE FROM 1 (MILD) TO 10 (HIGH):

a-	☐ NAUSEA :	0___1___2___3___4___5___6___7___8___9___10
b-	☐ VOMIT :	0___1___2___3___4___5___6___7___8___9___10
c-	☐ BLOATING, METEORISM:	0___1___2___3___4___5___6___7___8___9___10
d-	☐ REFLUX:	0___1___2___3___4___5___6___7___8___9___10
e-	☐ CONSTIPATION:	0___1___2___3___4___5___6___7___8___9___10
f-	☐ DIARRHEA:	0___1___2___3___4___5___6___7___8___9___10
g-	☐ ABDOMINAL PAIN:	0___1___2___3___4___5___6___7___8___9___10
h-	☐ OTHER (specify .....):	0___1___2___3___4___5___6___7___8___9___10

11. ☐ THE ADVERSE EFFECT APPEARED DESPITE ADHESION TO THE PERSONALIZED NUTRIOTIONAL RECOMMENDATIONS.
12. ☐ THE ADVERSE EFFECT APPEARED AFTER CONSUMING A MEAL BEYOND THE AGREED QUANTITIES.
13. ☐ THE ADVERSE EFFECT APPEARED AFTER A LOSS OF CONTROL ON FOOD, ON EMOTIONAL BASE.
14. ☐ SYMPTOMS WERE MANAGED WITH DRUGS AND/OR PHYTOTHERAPY REMEDIES.
15. ☐ THE INTENSITY OF SYMPTOMS WERE SO HIGH THAT THE THERAPY WAS DISCONTINUED.

DATE:_____ NAME AND SURNAME (BLOCK LETTERS)_____

Figure 1: Self-reported questionnaire on the adverse events during the intervention period.

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Table 2: Comparison between Group A (diet) and Group B (diet + Liraglutide + OMNi-BiOTiC® METAtox).

	Gorup A	Group B	p-value
	(3 months diet)	(3 months diet + liraglutide + OMNi-BiOTiC® METAtox)	
Weigth(kg)	- 4.42 ± 3.66	- 8.08 ± 3.56	< 0.001
BMI	- 1.71 ± 1.47	- 3.02 ± 1.34	< 0.001
WC (cm)	- 4.98 ± 3.31	- 8.38 ± 3.65	< 0.001
WTR	- 0.03 ± 0.05	- 0.02 ± 0.06	n.s
WHtR	- 0.03 ± 0.02	- 0.04 ± 0.02	< 0.001
AV+ (liters)	- 2.21 ± 1.48	- 3.85 ± 1.84	< 0.001

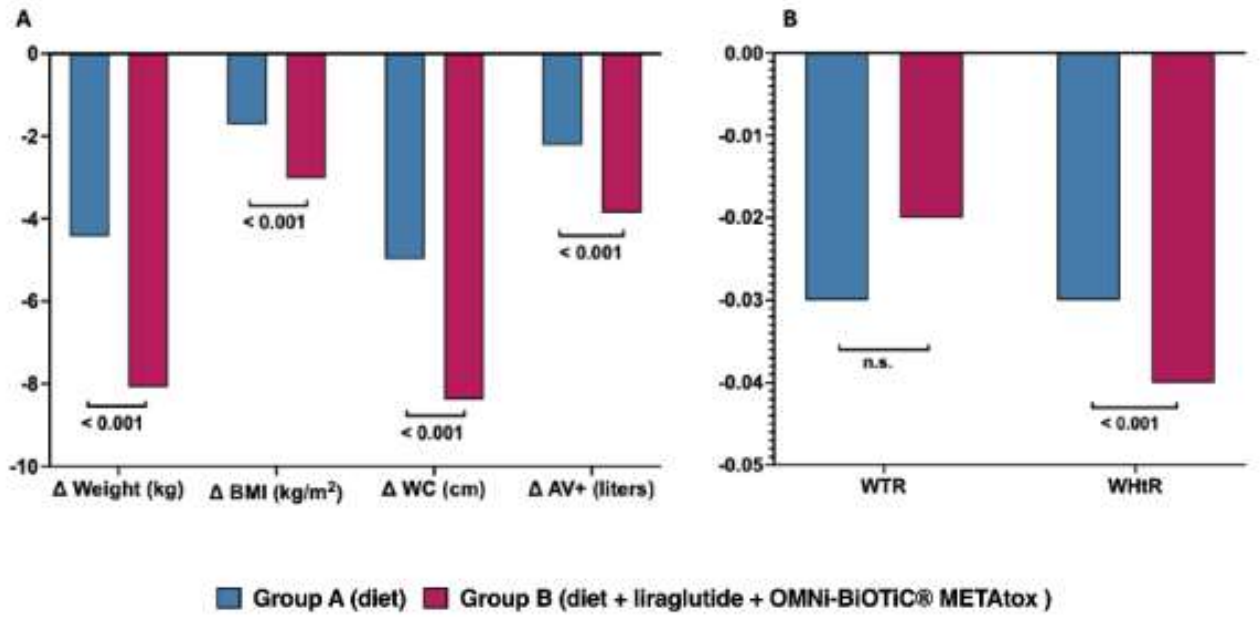

Figure 2: *Comparison between Group A (diet) and Gorup B (diet+ liraglutide 1.2 or1.8mg/day+* OMNi-BiOTiC® METAtox) in the clinical parameters analysed. (A) Comparison between weight, BMI, waist circumference (WC) and excessive abdominal volume (AV+); (B) comparison between waist-to-thigh ratio (WTR) and waist-to-height ratio (WHtR).

Comparison between our data and published data available from literature demonstrates that our patients have a reduction in weight, BMI and waist circumference comparable to the 1-year randomized study by Pi-Sunyer et al [50] (table 3).

Table 3: Comparison of the alterations in weight, BMI and WC in this study and a dataset of 731 patients published in Pi-Sunyer et al. 2015. The reduction in all the parameters analyzed is comparable between out three months intervention with low dose liraglutide compared to a 13 months high dose treatment.

	Liraglutide (1.2-1.8 mg/day) + OMNi-BiOTiC® METAtox (3 months)	Pi-Sunyer (3 mg/day) (13 months)
Weigth(kg)	- 8.08 ± 3.56	- 8.4 ±7.3
BMI	- 3.02 ± 1.34	- 3.0 ± 2.6
WC (cm)	- 8.38 ± 3.65	- 8.2 ± 7.3

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ith comparable therapeutic outcomes to Pi-Sunyer et al, 59.3 % of our patients exhibited only mild to moderate gastro-intestinal side effects of short duration, at the beginning of therapy or at dosage rise, but no patient had to discontinue the therapy due to severe side effects. On the contrary, in the Pi-Sunyer study, adverse events occurred in 80.3 % of the patients, 94% of which were gastro-intestinal of mild to moderate intensity, and 159 patients (6.4%) discontinued therapy due to the appearance of high intensity gastro-intestinal events, incompatible with therapy continuation (table 4).

Table 4: Gastro-intestinal (G.I.) adverse events (AE) comparison between Liraglutide 1.2-1.8 mg/day plus multispecies probiotic and liraglutide 3 mg/day according to Pi-Sunyer et al.

	Liraglutide (1.2-1.8 mg/day) + OMNi-BiOTiC® METAtox	Pi-Sunyer (3 mg/day)
	(3 months)	(13 months)
G.I. AE (%)	59.3	94
Withdraw for G.I. AE (%)	0	6.4

Discussion

During this retrospective observational trial, our main aim was to investigate the effect of a multispecies probiotic formulation on the targeted as well as adverse effects of the GLP-1RA liraglutide. In addition, our secondary aim was to compare the effects of our low dose liraglutide intervention with high dose data from literature. We hypothesized that the synergistic effect between the multispecies probiotic and liraglutide allowed the latter to be used at lower and fixed dosages, with greater improvements compared to the control group and with equal results to the liraglutide therapy at 3 mg/day but with fewer side effects. Our results clearly show a comparable effect of low dose liraglutide (1.2-1.8 mg/day) in combination with the oral application of one sachet OMNi-BiOTiC® METAtox per day with the effects of a high dose intervention (3mg/day) described in PI-Sunyer et al. Nevertheless, the results from our approach show the same effect with fewer and, if any, significantly milder adverse events compared to a high dose intervention of liraglutide. We hypothesize that the main mechanisms underlying the synergy with liraglutide, which likely allows to maintain its efficacy at low dosages and with reduced side effects, are given by (1) restoration of eubiosis. The multispecies probiotic was able to modulate the dysbiotic environment, leading to an increased biodiversity of the gut microbiota as well as beneficial changes in the local pH. These changes were able to restore the balance of intestinal bacterial flora and counteract the proliferation of potential pathogens. (2) Improvement of the intestinal barrier and restoration of eubiosis promoted the proliferation of muciparous epithelial cells (goblet cells) and improved production of secretory IgA, leading to the recovery of immune defenses and improved tolerability to food antigens. (3) Due to the probiotic intervention, we hypothesize a reduction of chronic low-grade inflammation. The probiotic was able to modulate the cytokine production, promoting an increase in adipokines (anti-inflammatory) and reducing endotoxemia (LPS), resulting in a reduction of low-grade chronic inflammation, improvement of hepatic steatosis, insulin resistance and HOMA-IR [51, 52].

The use of liraglutide at low dosages leads to several advantages, such as (1) significant lower therapy costs, (2) better tolerability and fewer side effects, especially in subjects with particular visceral sensitivity or those with dyspepsia. (3) Reduction of the tachyphylaxis phenomenon on the receptor, leading to habituation to the dosage practiced. (4) Permission of selective and quality weight loss, with reduced risk of Sarcopenia. The low dosage of liraglutide allows, from one side a selective loss of abdominal-visceral fat (reduced AV+ and WC) and, on the other, it prevents excessive starvation (which occurs with the 3 mg dosage), which can lead to excessive loss of lean mass. Comparable studies with low dose of liraglutide but without the oral application of probiotics did not result in comparable beneficial effects on clinical parameters indicating the importance of probiotic intervention [51, 53, 54].

Conclusions

In conclusion, the use of a multispecies probiotic (OMNi-BiOTiC® METAtox) in combination with GLP-1RA (Liraglutide, Saxenda®) promotes the development of an intestinal microbiota capable of improving glucose metabolism, intestinal barrier integrity, decrease circulating bacterial endotoxin and systemic inflammation. This synergistic action is able to modulate the primary dysbiosis, already present in diabetic patients and individuals with obesity, and to prevent secondary dysbiosis related to Liraglutide-induced reduction of gastro-intestinal motility, with the consequent possibility of using the latter at lower dosages with the same efficacy but with fewer side effects, lower therapeutic costs, thus improving adherence to the rehabilitation program. Dysbiosis modulation lays the foundations for new therapeutic indications. Indeed, a probiotic "pre-treatment" lasting 7-10 days before starting drug therapy is advisable, in order to reduce primary dysbiosis and chronic inflammation, so as to create a favorable intestinal environment to "receive" the drug, with consequent lower chance of developing a secondary dysbiosis related to the slowing of gastro-intestinal emptying produced by the drug itself. In this study we show the first time the beneficial effects of the combination of an orally applied multispecies probiotic in combination with the GLP-1 analog Liraglutide. We demonstrate that a low dose treatment of Liraglutide in combination with the probiotic intervention has the full effect on the analyzed parameters

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weight, BMI, WC, WHtR and AV+ compared to a high dose study. Adverse events are significantly reduced in our study compared to other high dose studies, thus improving patient compliance and outcome. Comparable low dose studies with Liraglutide without probiotic intervention do not come close to the positive effects in our study. A large scale, prospective and placebo-controlled randomized trial is required and planned, to verify these preliminary but promising results.

Author Contributions

MM conducted medical examinations, collected data and wrote the manuscript, ED'A did bibliography/reference research, LV collected data and followed nutritional behavior, DA and MS conducted the statistical analysis, PDC conducted medical examination, collected data, designed and supervised the study, wrote the manuscript.

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No funding, the study was conducted in a private facility; every patient paid for its own treatment.

Institutional Review Board Statement

It's a retrospective observational study to evaluate the efficacy and quality of new therapeutic models for obesity. Every data collected is anonymous.

Informed Consent Statement

Every patient signed an informed consent for the therapies with right of anonymity for the use of personal data for retrospective analysis.

Conflicts of Interest

Paolo de Cristofaro is a founding partner of Nubentech srl. Other authors declare no conflicts of interest.

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