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Original article

Evaluation of the tolerability and efficacy of a non-competitive, reversible inhibitor of the α-amylase and α-glucosidase enzymes with a specific, standardized polyphenolic composition on the modulation of postprandial glycemic peaks in overweight patients with impaired fasting glucose

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Summary. The prevalence of impaired fasting glucose (IFG) in the general population presents a significant clinical challenge given the high rate of progression to full-blown diabetes and the associated increase in cardiovascular risk and other complications, and justifies the need for early corrective intervention based on lifestyle changes supported by supplements to modulate postprandial glycemic peaks. This open-label study, based on a cross-over model, was conducted on a sample of 25 overweight patients with IFG taking part in a standardized lifestyle intervention program in order to analyze its effectiveness in modulating postprandial glycemic peaks as well as the gastrointestinal tolerability of a specific, standardized polyphenolic supplement (extracted from *Ascophyllum nodosum* and *Fucus vesiculosus*). The trend in capillary blood glucose values measured in patients enrolled in the study confirms the ability of the product used to modulate glycemic fluctuations both after ordinary meals consumed in real-life conditions and after a standard meal with controlled intake of carbohydrates, compared to observed values after consuming the same meals without supplements. The homogeneity of the glycemic values observed three hours after the standard meal, both with and without supplementation, also confirms the absence of late hypoglycemic effects.

Key words: impaired fasting blood glucose (IFG), diabetes mellitus, lifestyle intervention, α-amylase, α-glucosidase, *Ascophyllum nodosum*, glycemic peaks, *Fucus vesiculosus*

Introduction

The incidence of Type 2 Diabetes Mellitus is steadily increasing worldwide. According to ISTAT data for 2015, in Italy approximately 5.4% of the population were diabetic, compared with 3.9% in 2001 (1). A further group is affected by impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). Although these individuals are not yet technically diabetic, they have started on the path towards the full phenotypic expression of the disease. According to data published by the International Diabetes Foundation (IDF), the prevalence of IFG in the general population is around 6% (2). Ten years on the first glycemic disorders , the rate of conversion to diabetes is around 7.6% (3), but the progressive deterioration of glycemic variability indices (including postprandial glycemia) is in itself associated with increased cardiovascular risk (4) while the control of the same indices reduces the incidence of nephropathy and retinopathy

(5), justifying the need for early corrective intervention.

Often these patients are overweight or obese, have a sedentary lifestyle, and present the hallmarks of what has been called metabolic syndrome. The modulation of postprandial glycemic peaks is one of the cardinal objectives of the treatment of these patients and represents – together with weight reduction – the most effective instrument to counter the secondary hyperinsulinism typical of this clinical picture. The most effective therapeutic tools that can be used for this purpose include personalized, targeted physical activity and a carbohydrate-controlled diet. This approach can be supplemented by the use of phytotherapic formulations which act at various levels on glucose metabolism.

The effect of a carbohydrate-controlled feed intake on postprandial insulin and glycemic peaks in subjects with IFG is widely confirmed and solidly documented in the literature: there is substantial consensus on the importance of controlling the quantity and quality of carbohydrate intake, with particular reference to the index and glycemic load of meals, and how to intervene to achieve this goal (6).

With regard to the importance of a regular physical exercise regime and the way in which it is administered, the evidence is substantial. Here too there is broad consensus regarding minimum activity levels to propose, generally estimated to be in the order of 150 minutes a week of moderate aerobic activity or 75 minutes of vigorous activity, divided into at least three days and with breaks not exceeding two consecutive days. Interval training (7) is a possible alternative in trained subjects. Recently, a number of authors have demonstrated the greater effectiveness, in terms of controlling postprandial glycemic peaks, of a combination of a regular aerobic exercise regime with preprandial hits of high-intensity cardiovascular activity of up to ten minutes in duration, compared to aerobic activity alone (8).

With regard to the use of phytotherapies in the control of glycemia, several products with different mechanisms of action and which therefore act at different levels and with different degrees of effectiveness on the glucose metabolism are now available. Our study was conducted using a readily available product (Gdue™, Aesculapius Farmaceutici Srl - Brescia, Italy) with a specific, standardized polyphenolic composition (extracted from *Ascophyllum nodosum* and Fucus vesiculosus in a 95:5 ratio, at a total dosage of 250 mg per capsule, in addition to 6 mcg of chromium picolinate); the innovative technology used in its manufacture reduces the presence of iodine, which is naturally present in abundance in algal derivatives, to just 75 mcg of iodine per capsule. The polyphenols (florotannins) contained in the product have been shown to inhibit, in vitro and in mouse models, the activity of the intestinal enzymes α-amylase and α-glucosidase, slowing the absorption times of simple and complex carbohydrates and reducing postprandial glycemias accordingly in a dose-dependent manner (9) with a non-competitive, reversible mechanism of action. Another interesting characteristic of its mechanism of action is that it is not systemic, being expressed at the tissue level in the duodenum and on the brush border where the inhibiting enzymes are positioned, thus not interfering with other substances and ongoing therapies. At the recommended dosage of two / three capsules per day the product induces florotannin levels 25 to 50 times greater in intestinal fluids than inhibitory concentrations defined in vitro (10). Studies conducted on humans have demonstrated the ability of the product to modulate the assimilation of sugars introduced with the diet with a consequent reduction of postprandial glycemic peaks and secondary insulinemic response (normally accentuated in patients with IFG), which in turn allows a more physiological modulation of postprandial glycemia in the hours following a test meal (11). Treatment with the same product also reduced fasting blood sugar and insulinemia and abdominal circumference in obese and diabetic patients treated for 6 months (12).

Aim and design of the study

The aim of the study was to analyze the efficacy on modulation of postprandial glycemic peaks and the gastrointestinal tolerability of a supplement already on the market, with a specific, standardized polyphenolic composition (extracted from *Ascophyllum nodosum* and Fucus vesiculosus) in overweight patients with IFG following a standardized lifestyle intervention program.

The effectiveness of the supplement-based strategy was evaluated by comparing pre- and postprandial glycemic values measured in patients following only a lifestyle intervention program and the corresponding values measured by combining supplementation with the ongoing lifestyle intervention.

Given the small sample size, the study was built according to an open-label, cross-over design, with a duration of two weeks and with each patient acting as their own control. In the first week (without supplementation) and in the second week (with supplementation) patients measured their capillary blood glucose values before and two hours after the three ordinary daily meals (breakfast, lunch and dinner) and a standard meal (lunch) with a caloric and glycemic intake which was controlled and calculated by means of a specific program, using the Souci-Fachmann-Kraut food composition values (13) (Table 1). Capillary blood glucose was measured three hours after the meal in order to evaluate to what extent the supplement with extracts of *Ascophyllum nodosum* and *Fucus vesiculosus* is able to modulate glycemic fluctuation for some time after the meal itself.

Table 1. Detailed composition of the standardized test meal

Kcal	892
Total protein	46 gr: 20.7%
Isoleucine	2323 mg
Leucine	3811 mg
Lysine	3501 mg
Methionine	1021 mg
Phenylalanine	2206 mg
Threonine	1993 mg
Tryptophan	514 mg
Valine	2514 mg
Arginine	2699 mg
Total lipids	32 gr: 32.6%
Saturated	6117 mg: 6.2%
Monounsaturated	16823 mg: 17.0%
Polyunsaturated	3092 mg: 3.1%
Cholesterol	138 mg
Omega-6	2775 mg: 2.8%
Omega-3	317 mg: 0.3%
Carbohydrates	104 gr: 46.5%
Simple sugars	17 gr: 7.5%
Fiber	9 gr
Sodium	511 mg
Calcium	246 mg
Phosphorus	577 mg
Potassium	1227 mg
Chlorine	193 g
Magnesium	101 mg
Iron	7719 microg
Zinc	6866 microg
Copper	550 microg
Selenium	24 microg
Iodine	10.5 microg
Manganese	1112 mg
Chrome	10.9 microg
Fluor	145 microg
Vit. B1	354 microg
Vit. B2	442 microg
Vit. B3	8782 microg
Pantotenic acid	2107 microg
Biotin	17 microg
Vit. B6	656 microg
Vit. B12	2700 nanog
Vit. C	27 mg
Folate	163 microg
Vit. A	383 microg
Vit. D	65 nanog
Vit. K	7 microg
Vit. E	3722 microg
Alcohol	0 gr

Statistics

The initial hypothesis of the study was that it would be possible to demonstrate the efficacy of a polyphenol-based supplementation strategy using extracts from *Ascophyllum nodosum* and *Fucus vesiculosus* in the control of postprandial glycemia both after standard meals and test meals with controlled glucidic intakein patients with IFG already undergoing a controlled lifestyle intervention. Specifically, after glucose supplementation, lower glucose levels were expected two hours after all meals, with no excessive reduction in blood glucose levels three hours after the standard meal. The data were statistically analyzed using version 24 of IBM SPSS statistical software. A descriptive statistical analysis of the glycemic values of the standard meal and the test meal was performed, with and without supplementation. In particular, the following groups of meals were analyzed: normal meal before lunch, normal meal after 2 hours, and, on the day of the standardized test meal, breakfast time, before lunch, after 2 hours and 3 hours after the standardized test meal. Furthermore, a non-parametric analysis of independent samples (U-Mann-Whitney test) was performed, comparing the various meals with and without supplementation, with a level of significance $p \leq 0.05$.

Patients and methods

The study was conducted on a sample of 25 patients with IFG. The patients were male and female, aged between 19 and 75, with a body-mass index (BMI) of between 25 and 30. They were selected randomly from a larger population of patients who met the inclusion criteria attending any of a network of nutrition clinics in the province of Parma (Italy).

The primary inclusion criteria were a BMI of between 25 and 30 and a diagnosis of IFG within the last year made on the basis of venous samples showing fasting plasma glucose values between 100 and 125 mg / dl.

Criteria for exclusion from the study were a BMI of less than 25 or more than 30, any major pathologies (including cardiovascular, nephrological, hepatic or neoplastic conditions), pregnancy and any pharmacological treatments that could potentially interfere with the parameters under consideration.

All subjects enrolled in the study were informed in detail about the methods. All of them completed and signed an informed consent form and received isocaloric-based nutritional guidelines and a training program based on an aerobic exercise regime (involving either walking or using an exercise bike) lasting 30 minutes, to be performed mid-morning or mid-afternoon, at least two hours after meals. After one week of lifestyle intervention, the aim of which was to correct their nutritional intake in qualitative terms and not to induce weight loss, patients measured capillary blood glucose levels before and after three ordinary meals (breakfast, lunch and dinner consumed during the weekend). Subsequently, on Sundays or on a working day agreed with the patients, they repeated the blood glucose measurements in the morning on an empty stomach, immediately before a standard meal and then two and three hours after the meal.

The patients then continued with no changes to the lifestyle intervention described above, adding the commercially-available polyphenol-based supplement with extracts of *Ascophyllum nodosum* and *Fucus vesiculosus* and taking three capsules per day (one capsule 30 minutes before each of the three main meals) for another week, and taking the same measurements.

In addition to the self-measurement of capillary blood glucose levels using Accu-chek Aviva sticks and reflectometers with which all patients were provided at the beginning of the study, the height and weight of all participants in the study were measured on enrolment (T0), at the end of the first week of intervention (T1) and at the end of the study (T2). During the study, weight fluctuations were tolerated within a range of one kilogram gained or lost at times T1 and T2 from the baseline: any greater fluctuations led to the data for the patient concerned being excluded from the subsequent statistical analysis.

Results

The final sample of subjects enrolled in the study consisted of 25 patients (13 males and 12 females) with an average age of 58.8 ± 8.4 and a BMI of 26.6 ± 2.9.

2 of the enrolled subjects did not collect the data in accordance with the protocol. 23 subjects completed the study; however, for statistical purposes data were used from the 22 patients whose weight changes during the study period remained within the limits set by the protocol.

Table 2 shows capillary blood glucose levels measured by the patients before and two hours after the three ordinary weekly meals (breakfast, lunch and dinner), while Table 3 shows the values measured before and after breakfast and then before and two and three hours after the standard carbohydrate-controlled meal. Capillary blood glucose levels measured in the two groups before ordinary meals were 103.1 ± 17.8 mg / dl without supplementation vs 104.4 ± 17.7 mg / dl with supplementation and did not significantly differ in the two groups. The same values measured two hours after ordinary meals were 130.3 ± 31.6 mg / dl without

Table 2. Capillary blood glucose values measured before and two hours after ordinary meals (breakfast, lunch and dinner), with and without supplementation. The differences between the postprandial values (two hours after the meal) with and without integration are statistically significant.

	Before ordinary meals without supplement	Before ordinary meals with supplementation	After 2 hours of ordinary meals without supplementation	After 2 hours of ordinary meals with supplementation
Number of observations	66	66	66	66
Average (mg/dl)	103.18±17.807	104.41±17.738	130.32±31.66	116.12±24.23
	p=0,67 (ns)		p<0,05 (significative)	

Table 3. Capillary blood glucose values measured at 4 different times on the day of standardized meal, with and without supplementation. Blood glucose values differ significantly in observations taken two hours after eating (p <0.05). This difference receded in the subsequent observation.

	Breakfast without supplementation	Breakfast with supplementation	Before lunch without supplementation	Before lunch with supplementation	2 hours after meal without supplementation	2 hours after meal with supplementation	3 hours after meal without supplementation	3 hours after meal with supplementation
Number of observations	22	22	22	22	22	22	22	22
Average (mg/dl)	104.95±11.71	111.86±13.5	100.8±11.6	104.2±16.4	136.09±29.3	116.2±29.1	124.9±32.6	111±18.5
	p=0.07 (ns)		p=0.82 (ns)		p<0.05 (significant)		p=0.34 (ns)	

supplementation and 116.1 ± 24.2 mg / dl with supplementation, thus exhibiting a statistically significant difference (p <0.05) between the two groups (Fig. 1). Regarding the trend in blood glucose levels before and after the standard meal compared to homogeneous values in the two groups both at breakfast (104.9 ± 11.1 mg / dl vs 111.8 ± 13.5 mg / dl; p = 0.07 ns) and before the meal (100.8 ± 11.6 mg / dl vs 104.2 ± 16.4 mg / dl; p = 0.8 ns), the values measured two hours after the meal were 136.0 ± 29.3 mg / dl without supplementation vs

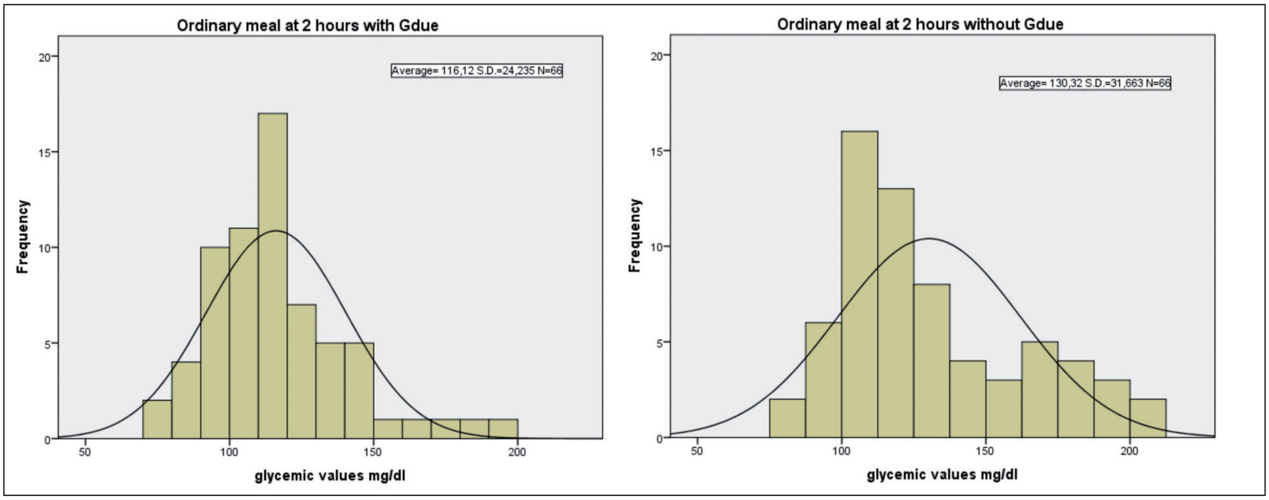

Figure 1. Changes in blood sugar levels after ordinary meals. Capillary blood glucose values measured two hours after ordinary meals show a statistically significant difference (p <0.05) between the two groups.

116.2 ± 22.2 mg / dl with supplementation with a statistically significant difference ($p < 0.05$) between the two groups (Fig. 2). Three hours after the meal the difference between the two groups was cancelled out (124.9 ± 32.6 mg / dl vs 111.0 ± 18.5 mg / dl; p = 0.34 ns) (Fig. 3). Specifically, glycemic values measured in individual patients within three hours of the meal were never lower than 90 mg / dl.

The trend in capillary blood glucose levels measured in the patients enrolled in the study thus confirms – in accordance with our initial thesis – the ability of a product with a specific, standardized polyphenolic composition (extracted from *Ascophyllum nodosum* and *Fucus vesiculosus*) such as the one we used, to modulate glycemic fluctuations both after ordinary meals consumed in real-life conditions and after a standard carbohydrate-controlled meal compared to what is observed after the same meals have been consumed in patients with IFG already undergoing a standardized lifestyle correction program (Fig. 4).

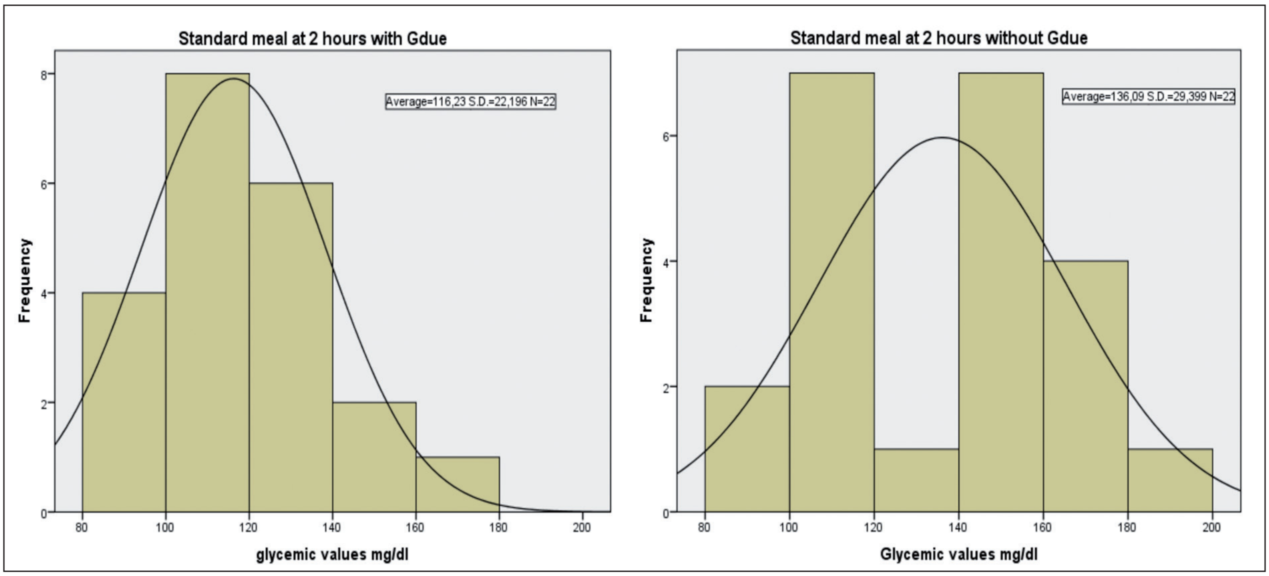

Figure 2. Blood glucose levels after the standardized test meal: blood glucose levels measured two hours after the meal were significantly lower after intake of the supplement ($p < 0.05$).

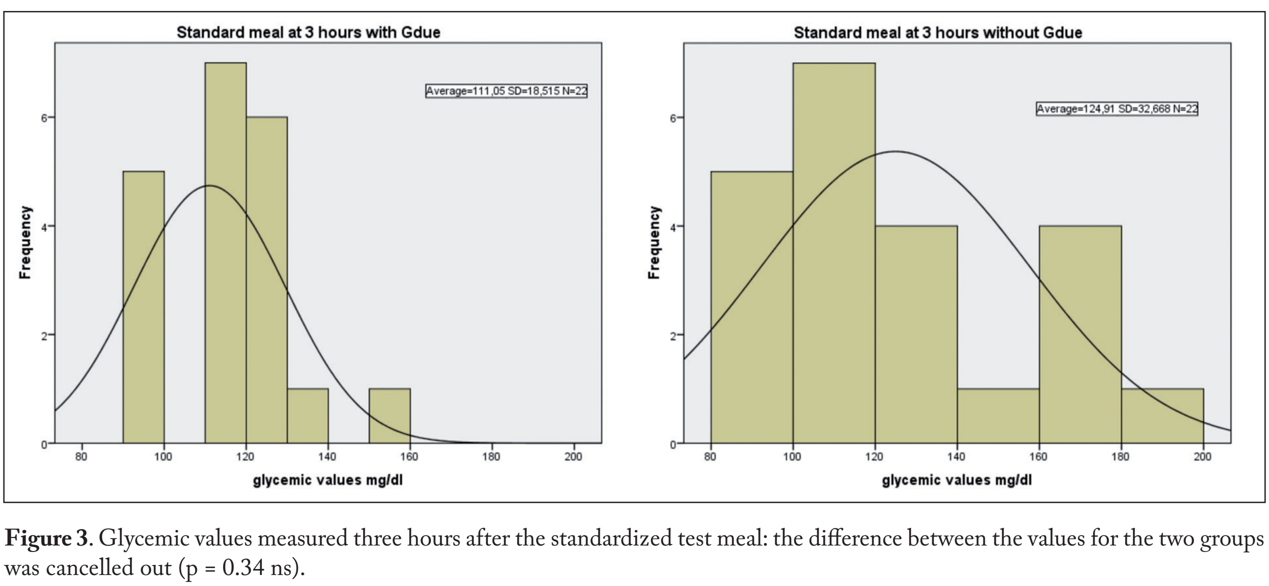

Figure 3. Glycemic values measured three hours after the standardized test meal: the difference between the values for the two groups was cancelled out (p = 0.34 ns).

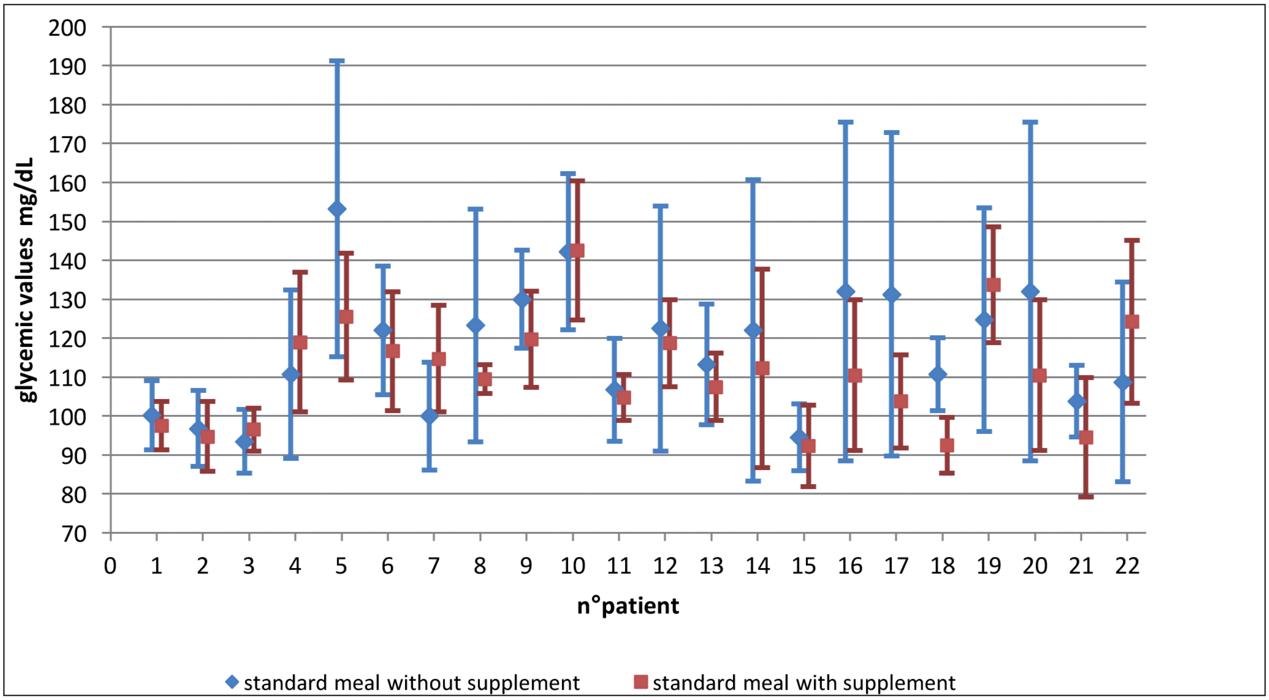

Figure 4. Mean values ± 1 SD of blood sugar after standardized meal, showing a clear difference between the values measured with and without supplementation.

The homogeneity of the glycemic values observed three hours after the standard meal, both with and without the polyphenol-based supplement extracted from *Ascophyllum nodosum* and *Fucus vesiculosus*, also confirms the absence of late hypoglycemic effects.

The tolerability of the product was found to be satisfactory. The data are reported in Table 4: of the 23 subjects who completed the study, only three reported slight abdominal discomfort of an entity not such as to determine the abandonment of the study protocol.

Conclusions

The steady increase in new cases of diabetes and other changes in glucose metabolism such as impaired fasting glucose and impaired sugar tolerance confirms the substantial failure of contrast strategies implemented in recent years, despite the well-known physiopathological mechanisms that underlie the appearance and evolution of these metabolic alterations. The combined effect of a regular physical activity regime,

Table 4. Side effects reported during the study

Initial sample	25 patients
Number of patients who completed the study	23
Side effects reported:	
- none	21 patients
- feeling of bloating / mild abdominal discomfort	2 patients
- feeling of bloating / mild or severe abdominal discomfort	none
- nausea / loss of appetite	none
- asthenia	none

variously structured between alternating phases of aerobic exercise and high-intensity exercise depending on the characteristics of the subject, and a varied and balanced diet is widely documented, but despite this it remains difficult to transform this knowledge into appropriate behavior in the majority of the population.

That said, and given that the intervention on lifestyle remains central, the growing attention of the research world, the media and the general public towards the health benefits of supplements and herbal products, can be a useful tool in promoting of healthier lifestyles.

For this type of intervention to be justified, it is essential that the proposed products are effective, safe, correctly titrated and used in the context of a rational phytotherapeutic approach. This involves a careful evaluation of the cost-benefit ratio of the individual active ingredients and of the complex combinations of substances found in products of natural origin.

Among the many products offered by phytotherapy, polyphenols extracted from *Ascophyllum nodosum* and *Fucus vesiculosus* have already proved effective in modulating digestive enzymes. Their use in the control of postprandial glycemic peaks thus has a specific rationale, as is confirmed by our study. Despite several limitations related to the small sample size and the design of the study, the data collected seem to confirm the efficacy of a product such as the one we studied on the optimization of glycemic control in subjects with IFG.

Larger, more robust studies will be required in order to confirm the data observed. However, our results would seem to show that polyphenols extracted from *Ascophyllum nodosum* and *Fucus vesiculosus* offer an interesting risk/benefit ratio and can be proposed as an effective and well-tolerated tool for modulating postprandial glycemic peaks in overweight patients with IFG who are already following an integrated lifestyle intervention program.

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