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RESEARCH ARTICLE

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Ascophyllum nodosum and *Fucus vesiculosus* on glycemic status and on endothelial damage markers in dysglicemic patients

Giuseppe Derosa[1,2,3] | Arrigo F.G. Cicero[4] | Angela D'Angelo[2] | Pamela Maffioli[1]

[1] Centre of Diabetes and Metabolic Diseases, Department of Internal Medicine and Therapeutics, University of Pavia and Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

[2] Laboratory of Molecular Medicine, University of Pavia, Pavia, Italy

[3] Center for Prevention, Surveillance, Diagnosis and Treatment of Rare Diseases, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

[4] Department of Medical and Surgical Sciences, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

Correspondence
Giuseppe Derosa, MD, PhD, FESC, Department of Internal Medicine and Therapeutics, University of Pavia, Fondazione IRCCS Policlinico San Matteo, Pavia, P. le C. Golgi, 2-27100 Pavia, Italy.
Email: giuseppe.derosa@unipv.it

The aim of this study was to evaluate a nutraceutical combination containing polyphenols extracted from *Ascophyllum nodosum* and *Fucus vesiculosus* and chromium picolinate on glyemic status; secondary outcomes were considered the changes on endothelial markers. We randomized 65 dysglycemic patients to placebo or the nutraceutical agent for 6 months. We evaluated fasting plasma glucose (FPG), postprandial plasma glucose (PPG), HbA_{1c}, fasting plasma insulin, homeostatic model assessment (HOMA) index, high sensitivity C-reactive protein (Hs-CRP), tumor necrosis factor-α (TNF-α), and adhesion molecules. At baseline and at 3 and 6 months, all patients underwent an oral glucose tolerance test. We recorded a reduction of HbA_{1c}, FPG, PPG, and HOMA-IR compared with placebo ($p < 0.05$). After 6 months, 18.2% of patients retuned to a normal glycemic status in the nutraceutical group versus 0 patients in placebo group ($p < 0.05$); 69.7% were classified as impaired fasting glycemia and 12.1% as impaired glucose tolerance in the nutraceutical group versus 17.2% and 82.8 in placebo group ($p < 0.01$) for both. A reduction of Hs-CRP and TNF-α was recorded with the nutraceutical. The administration of a nutraceutical combination containing *A. nodosum* and *F. vesiculosus* can be helpful in improving insulin sensitivity and glycemic status. Larger randomized studies are required to confirm the positive effects of these agents.

KEYWORDS

Ascophyllum nodosum, dysglycemia, *Fucus vesiculosus*, nutraceutical

1 | INTRODUCTION

Dysglycemia is one of the most important risk factors for diabetes and contributes to an increased risk of developing cardiovascular diseases. In the general population, the relationship between complications related to dysglycemia, including cardiovascular problems, is linear and continuous; the impact of cardiovascular events is closely related to the deterioration of glycemic control. This association appears stronger when considering the levels of postprandial glucose (PPG; Bartnik, Norhammar, & Rydén, 2007). Postprandial glycemia, in fact, is considered an independent cardiovascular risk factor and a powerful inducer of endothelial damage (Derosa et al., 2009, 2010a, 2010b).

Dysglycemia includes three conditions: impaired fasting glucose (IFG), impaired carbohydrate tolerance (IGT), both can evolve into type 2 diabetes mellitus (Gerstein, 2010).

Among nutraceuticals, a nutraceutical with a specific polyphenolic composition (extracted from *Ascophyllum nodosum* and *Fucus vesiculosus* in a ratio of 95/5) and chromium picolinate could have a good action on glycemia. The polyphenolic composition is represented by phlorotannins, able to inhibit α-amilase, and α-glucosidase with an important hypoglycemic action in vivo (Paradis, Couture, & Lamarche, 2011; Roy et al., 2011) and in particular PPG. Phlorotannins slow carbohydrate absorption with a not competitive (not focalized on catalitic site in competition with the substrate) and reversible mechanism of inhibition of the enzymes involved in carbohydrates degrading (Paradis et al., 2011). The inhibiting action towards the activity of these enzymes results, in animal models (rats), in a reduction of glycemia and insulinemia after administration of amids and glucose.

In this context, we planned to carry out a randomized study to evaluate the efficacy and safety of a nutraceutical agent containing

extracted from *A. nodosum* and *F. vesiculosus* in a ratio of 95/5 and chromium picolinate (Gdue® marketed by Aesculapius) in a sample of Caucasian patients with dysglycemia. The primary outcome was to evaluate the effects of this nutraceutical combination on fasting plasma glucose (FPG), PPG, and glycemic status; secondary outcomes were considered the changes on some endothelial damage markers.

2 | MATERIALS AND METHODS

2.1 | Study design

This 6-months, double-blind, randomized, placebo-controlled, clinical trial was conducted at the Department of Internal Medicine and Therapeutics, University of Pavia (Pavia, Italy), among patients attending the Centre for the Treatment of Diabetes and Metabolic Diseases.

The study protocol was approved by the local institutional ethical committee and was conducted in accordance with the 1994 Declaration of Helsinki (The Council for International Organisation of Medical Sciences, 1982) and its amendments and the Code of Good Clinical Practice. All patients provided written informed consent to participate in this study after a full explanation of the study had been given.

2.2 | Patients

Caucasian patients aged ≥18 years of either sex were eligible for inclusion in the study if they had FPG >100 mg/dl but <126 mg/dl. Subjects with high glucose levels variability in the year preceding the study (±20%), diabetic patients, patients with abnormal thyroid function, patients with hepatic impairment (defined as transaminases greater than three times the maximum limits laboratory), or renal impairment (defined as creatinine values greater than the upper limit of the laboratory) were excluded. Patients taking drugs potentially affecting glucose metabolism were also excluded. Also, subjects with cancer, chronic inflammatory diseases (rheumatic and infectious), and psychiatric diseases were excluded. Patients with serious cardiovascular disease (e.g., New York Heart Association class I-IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrollment were also excluded. Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were not enrolled in this trial.

2.3 | Diet and physical activity

All patients were already following an adequate diet and practicing physical activity. The controlled-energy diet (~600 kcal daily deficit) was based on NCEP-ATP III recommendations (Lichtenstein et al., 2006) that contained 50% of calories from carbohydrates, 30% from fat (<7% saturated, up to 10% polyunsaturated, and up to 20% monounsaturated), and 20% from proteins, with a maximum cholesterol content of 300 mg/day and 35 g/day of fiber. Standard diet advice was given by a dietitian and/or specialist physician. Individuals were also encouraged to increase their physical activity with a standardized physical aerobics exercise program by riding a stationary bicycle for 20 to 30 min, three to four times per week. Subjects were instructed to daily fill diaries about food and physical activity and to bring them to the Investigators to assess their compliance to lifestyle.

2.4 | Treatment

Patients were randomized to take placebo or a nutraceutical agent containing extracted from *A. nodosum* and *F. vesiculosus* in a ratio of 95/5 and chromium picolinate (Gdue® marketed by Aesculapius) for 6 months, in a randomized, double-blind, placebo-controlled design (Figure 1). The nutraceutical and placebo were self-administered three times a day, one tablet before the main meals. Both the nutraceutical and placebo were supplied as identical, opaque, tablets in coded bottles to ensure the blind status of the study.

Randomization was done using a drawing of envelopes containing randomization codes prepared by a statistician. Medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits. Throughout the study, we instructed patients to take their first dose of new medication on the day after they were given the study medication. At the same time, all unused medication was retrieved for inventory. All medications were provided free of charge.

2.5 | Assessments

Before starting the study, all patients underwent an initial screening assessment that included a medical history, physical examination, vital signs, a 12-lead electrocardiogram, measurements of waist circumference, abdominal circumference, hip circumference, body weight, height, body mass index (BMI), FPG, PPG, glycated hemoglobin (HbA_{1c}), fasting plasma insulin (FPI), HOMA index, high sensitivity C-reactive protein (Hs-CRP), tumor necrosis factor-α (TNF-α), soluble vascular cell adhesion protein-1 (sVCAM-1), soluble intercellular adhesion protein-1 (sICAM-1), and soluble E-selectin (sE-selectin). These parameters were assessed also after 3 and 6 months. At baseline and at 3 and 6 months, all patients underwent an oral glucose tolerance test (OGTT) with 75 g of glucose and glycemia determination at time 0 and after 120 min to evaluate if there was a condition of IFG, IGT, or type 2 diabetes mellitus.

All parameters were determined in fasting state, after a 12-hr overnight fast, in the plasma. Venous blood samples were taken for

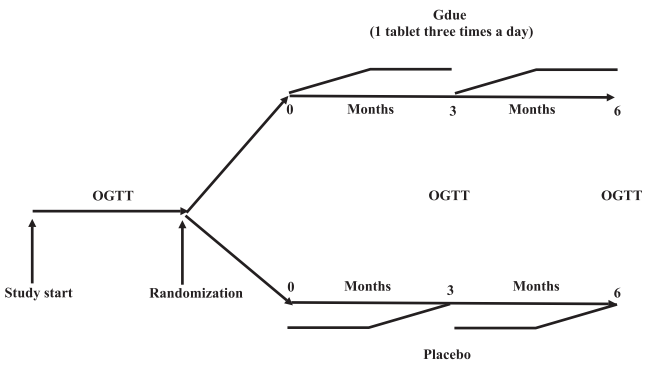

FIGURE 1 Study design. OGTT: oral glucose tolerance test

all patients between 8 and 9 a.m. and were drawn from an antecubital vein with a 19-gauge needle without venous stasis.

We used plasma obtained by addition of Na_2-EDTA, 1 mg/ml, and centrifuged at 3,000 *g* for 15 min at 4 °C. Immediately after centrifugation, the plasma samples were frozen and stored at −80 °C for no more than 3 months. All measurements were performed in a central laboratory.

BMI was calculated by the investigators as weight in kilograms divided by the square of height in meters. The estimate of insulin resistance was calculated by HOMA index with the formula: FPI (μU/ml) × FPG (mmol/L)/22.5, as described by Matthews et al. (1985).

Glycated hemoglobin level was measured by an HPLC method (DIAMAT, Bio-Rad, USA; normal values 4.2–6.2%), with intraassay and interassay coefficients of variation (CsV) of <2% (Bunn, Gabbay, & Gallop, 1978).

Plasma glucose was assayed by glucose-oxidase method (GOD/PAP, Roche Diagnostics, Mannheim, Germany) with intraassay and interassay CsV of <2% (European Diabetes Policy Group, 1999). Plasma insulin was assayed with Phadiaseph Insulin RIA (Pharmacia, Uppsala, Sweden) by using a second antibody to separate the free and antibody-bound ^{125}I-insulin (intraassay and interassay CsV 4.6 and 7.3%, respectively; Heding, 1972).

High-sensitivity C reactive protein was measured with use of latex-enhanced immunonephelometric assays on a BN II analyzer (Dade Behring, Newark, Delaware, USA). The intraassay and interassay CsV were 5.7% and 1.3%, respectively (Rifai, Tracy, & Ridker, 1999).

TNF-α level was assessed using commercially available ELISA kits according to manufacturer's instructions (Titer-Zyme EIA kit; Assay Designs, Ann Arbor, MI). Intraassay CsV were 4.5% for low- and 3.6% for high-concentration samples whereas the interassay CsV were 6.0% for low- and 11.8% for high-concentration samples, respectively (Zhang & Tracey, 1988).

Soluble vascular cell adhesion molecule-1 was assessed using commercially available ELISA kit according to manufacturer's instructions (R & D Systems, Minneapolis, MN, USA). The intraassay and interassay CsV were <10%, respectively (Peter, Weirich, Nordt, Ruef, & Bode, 1999).

Soluble intercellular adhesion molecule-1 was assessed using commercially available ELISA kits according to manufacturer's instructions (R & D Systems, Minneapolis, MN, USA). The intraassay and interassay CsV were <10%, respectively (Witkowska & Borawska, 2004).

Soluble E-selectin was determined using commercially available ELISA kits according to manufacturer's instructions (R & D Systems, Minneapolis, MN, USA). The intraassay and interassay CsV were 4.7% and 7.4%, respectively (Constans & Conri, 2006).

2.6 | Oral glucose tolerance test

All subjects drank a glass of water (200 ml), in which 75 g of glucose had been dissolved over a period of 5 min in the morning, between 8 and 9 a.m. after a 12-hr fast, and after dietary assessment to ensure a carbohydrate intake >150 g/day over the previous 3 days (American Diabetes Association, 2014). Normal physical activity was allowed over the previous 3 days. Smoking was not allowed during the test. Blood samples were collected in EDTA-containing tubes (Becton Dickinson, Meylan Cedex, France) through a venous catheter from an antecubital vein immediately before and at 120 min after the glucose load for the measurement of the considered parameters of the study.

2.7 | Statistical analysis

An intention-to-treat analysis was conducted in patients who had received ≥1 dose of study medication and had a subsequent efficacy observation. Considering as clinically significant a difference of at least the 10% compared with the baseline and an alpha error of 0.05, the actual sample size was adequate to obtain a power higher than 0.80 to detect a significant between-group difference in variables related to glycemia. Patients were included in the tolerability analysis if they had received ≥1 dose of trial medication after randomization and had undergone a subsequent tolerability observation. The null hypothesis that the expected mean of FPG, and PPG change from the end of the study did not differ significantly between placebo, and the nutraceutical combination was tested using analysis of variance and analysis of covariance models (Winer, 1971). Similar analyses were applied to the other variables. The statistical significance of the independent effects of treatments on the other variables was determined using analysis of covariance. A one-sample *t* test was used to compare values obtained before and after treatment administration; two-sample *t* tests were used for between-group comparisons. Statistical analysis of data was performed using the Statistical Package for Social Sciences software version 11.0 (SPSS Inc., Chicago, Illinois, USA). Data are presented as mean (*SD*). For all statistical analyses, $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Study sample

A total of 65 patients were enrolled in the trial. Of these, 31 were randomized to placebo and 34 to the nutraceutical agent. Sixty-two subjects completed the study; there were three patients who did not complete the study and the reasons for premature withdrawal included noncompliance to treatment or lost to follow-up. The characteristics of the patient population at study entry are shown in Tables 1 and 2.

3.2 | Anthropometric parameters and glycemic metabolism

No variations of BMI or circumferences were recorded with neither treatments (Tables 1 and 2).

A reduction of HbA_{1c} was recorded with the nutraceutical combination compared with placebo ($p < 0.05$); moreover, there was a reduction of FPG ($p < 0.05$), and PPG ($p < 0.01$) compared with baseline, and compared with placebo ($p < 0.05$ for both) with the nutraceutical combination. Regarding insulin resistance, there was a decrease

TABLE 1 Baseline 3 and 6 months data of patients during placebo treatment

Parameters N of pts (31)	Placebo group		
	Baseline	3 months	6 months
N	31	29	29
M/F	15/16	14/15	14/15
Smoking status (M/F)	7/8	7/7	7/7
Weight (kg)	79.1 ± 7.4	78.9 ± 7.2	78.5 ± 6.9
Height (m)	1.66 ± 0.08	–	–
BMI (kg/m^2)	28.8 ± 2.6	28.6 ± 2.4	28.1 ± 2.1
WC (cm)	89.2 ± 2.9	88.9 ± 2.6	88.6 ± 2.2
HC (cm)	102.6 ± 4.8	101.9 ± 3.6	101.2 ± 3.3
AC (cm)	94.7 ± 3.6	94.2 ± 3.4	93.9 ± 2.8
HbA_{1c} (%)	5.2 ± 0.5	5.3 ± 0.5	5.4 ± 0.6
FPG (mg/dl)	115.2 ± 7.1	116.4 ± 7.0	117.5 ± 6.8
PPG (mg/dl)	158.9 ± 15.6	159.7 ± 15.9	160.1 ± 16.4
FPI (μU/ml)	9.8 ± 3.3	9.9 ± 3.4	10.0 ± 3.7
HOMA index	2.8 ± 1.3	2.8 ± 1.4	2.9 ± 1.5
Hs-CRP (mg/L)	1.4 ± 0.9	1.3 ± 0.8	1.3 ± 0.8
TNF-α (ng/ml)	1.9 ± 0.7	1.9 ± 0.7	2.0 ± 0.8
sVCAM-1 (ng/ml)	465.8 ± 57.2	461.9 ± 56.1	472.1 ± 59.3
sICAM-1 (ng/ml)	149.1 ± 16.2	147.1 ± 15.9	144.9 ± 15.8
E-selectin (ng/ml)	24.9 ± 5.3	25.1 ± 5.4	25.6 ± 5.7

Note. Data are expressed as mean ± standard deviations. M: males; F: females; BMI: body mass index; WC: waist circumference; HC: hip circumference; AC: abdominal circumference; HbA1c: glycated hemoglobin; FPG: fasting plasma glucose; PPG: postprandial plasma glucose; FPI: fasting plasma insulin; HOMA: homeostatic model assessment; Hs-CRP: high sensitivity C-reactive protein; TNF-α: tumor necrosis factor-α; sVCAM-1: soluble vascular cell adhesion protein-1; sICAM-1: soluble intercellular adhesion protein-1; sE-selectin: soluble E-selectin.

of HOMA-IR with the nutraceutical combination compared to baseline ($p < 0.05$) and to placebo ($p < 0.05$; Tables 1 and 2).

3.3 | OGTT results

At baseline, 35.3% of patients were affected by IFG in the nutraceutical group versus 41.9% in placebo (*p* not significant), whereas 64.7% of patients were affected by IGT in the nutraceutical group and 58.1% in placebo group (*p* not significant). After 6 months, 18.2% of patients retuned to a normal glycemic status in the nutraceutical group versus 0 patients in placebo group ($p < 0.05$); at the end of the study, 69.7% were classified as IFG in the nutraceutical group versus 17.2% in placebo group ($p < 0.01$). In the nutraceutical group, 12.1% were classified as IGT (Figure 2) versus 82.8% in placebo group ($p < 0.01$).

3.4 | Cytokines

A reduction of Hs-CRP and TNF-α was recorded with the nutraceutical combination compared with baseline ($p < 0.05$ for both) and compared with the placebo group ($p < 0.05$ for both). No variations were observed for sVCAM-1, sICAM-1, and E-selectin in neither group (Tables 1 and 2).

4 | DISCUSSION

Our results are in line with what reported by De Martin et al. (2017); these authors also recorded an improvement of circumferences and blood glucose with this nutraceutical combination. The most important data, however, in authors opinion, is the regression to IFG from IGT and the regression form IFG to normal glucose tolerance (NGT) in the nutraceutical group. The positive results on glycemic control observed in our study can be due to the inhibiting action of the polyphenolic composition (extracted from *A. nodosum* and *F. vesiculosus*) towards enzymatic activities, in an acarbose-like mechanism. The ability of a phytocomplex obtained from these algae to inhibit both enzymes has already been demonstrated by Roy et al. (2011) and confirmed by Gabbia et al. (2017) who showed that the administration of the extract in a diet particularly rich in fat in mice is associated with a delay in carbohydrate digestion but also with a decrease in its assimilation. Reducing PPG with the nutraceutical, probably, leads to a minor work for the β-cells and a consequent longer preservation of β-cell function. Regarding the effects of the nutraceutical on insulin resistance, the improvement of HOMA-IR (calculated as [FPG × FPI]/22.5) is due more to a reduction of FPG than a reduction of FPI. Regarding endothelial damage, there is evidence that supports the use of sCAMs as potential biomarkers of endothelial activation, as showed by Kjaergaard, Dige, Krog, Tønnesen, and Wogensen (2013). These authors showed a significant positive correlation between the levels of ICAM-1 and sICAM-1 and between the levels of VCAM and sVCAM-1 in both the dose-response

TABLE 2 Baseline 3 and 6 months data of patients during Gdue treatment

Parameters N of pts (34)	Gdue group Baseline	3 months	6 months
N	34	34	33
M/F	18/16	18/16	17/16
Smoking status (M/F)	9/7	9/7	9/7
Weight (kg)	80.7 ± 7.9	80.3 ± 7.6	79.2 ± 7.5
Height (m)	1.67 ± 0.09	–	–
BMI (kg/m^2)	28.9 ± 2.7	28.8 ± 2.6	28.4 ± 2.2
WC (cm)	89.9 ± 3.2	89.5 ± 3.1	89.3 ± 3.0
HC (cm)	103.2 ± 5.4	102.7 ± 4.9	102.4 ± 4.3
AC (cm)	95.6 ± 3.9	94.8 ± 3.5	94.1 ± 3.2
HbA_{1c} (%)	5.1 ± 0.5	5.0 ± 0.5	4.9 ± 0.4***
FPG (mg/dl)	113.2 ± 6.4	109.2 ± 6.2	104.3 ± 5.9****
PPG (mg/dl)	157.8 ± 15.2	149.7 ± 13.4*	141.2 ± 11.5*****
FPI (μU/ml)	9.6 ± 3.1	9.3 ± 3.2	9.0 ± 2.8
HOMA index	2.7 ± 1.2	2.5 ± 1.1	2.3 ± 0.9****
Hs-CRP (mg/L)	1.4 ± 0.9	1.2 ± 0.7	1.0 ± 0.4****
TNF-α (ng/ml)	1.8 ± 0.6	1.6 ± 0.5	1.5 ± 0.3****
sVCAM-1 (ng/ml)	442.7 ± 52.6	431.7 ± 49.3	412.8 ± 45.3
sICAM-1 (ng/ml)	147.2 ± 15.9	141.6 ± 15.1	137.8 ± 14.6
E-selectin (ng/ml)	24.0 ± 5.1	23.8 ± 4.7	22.3 ± 4.1

Note. Data are expressed as mean ± standard deviations. M: males; F: females; BMI: body mass index; WC: waist circumference; HC: hip circumference; AC: abdominal circumference; HbA1c: glycated hemoglobin; FPG: fasting plasma glucose; PPG: postprandial plasma glucose; FPI: fasting plasma insulin; HOMA: homeostatic model assessment; Hs-CRP: high sensitivity C-reactive protein; TNF-α: tumor necrosis factor-α; sVCAM-1: soluble vascular cell adhesion protein-1; sICAM-1: soluble intercellular adhesion protein-1; sE-selectin: soluble E-selectin.

*$p < 0.05$ vs. baseline.

**$p < 0.01$ vs. baseline.

***$p < 0.05$ vs. placebo group.

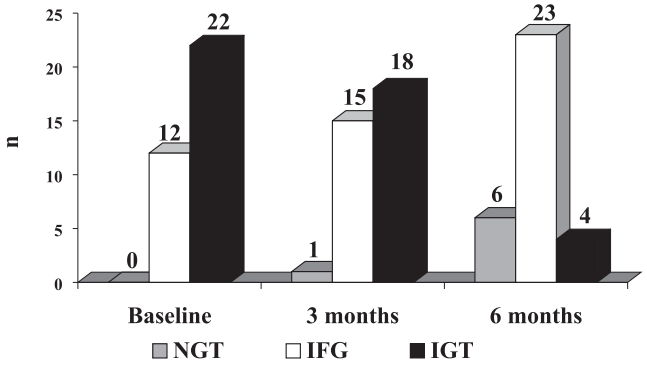

FIGURE 2 Results after OGTT at baseline and after 3 and 6 months in patients treated with Gdue. IFG: impaired fasting glucose; IGT: impaired carbohydrate tolerance; NGT: normal glucose tolerance; OGTT: oral glucose tolerance test

and time-response experiments, and a positive correlation between the levels of E-selectin and sE-selectin was observed in the time-response experiment. In our study, we did not record a change of these markers with the nutraceutrical.

Considering that Baldrick et al. (2018) showed that consumption of the seaweed (poly)phenols resulted in a modest decrease in DNA damage, but only in a subset of the total population who were obese, and that there were no significant changes in CRP, antioxidant status, or inflammatory cytokines, we wanted to evaluate the effects on inflammation also in dysglicemic patients. Differently form Baldrick et al., there was an improvement of Hs-CRP and TNF-α values. TNF-α was the first adipose-secreted product proposed to represent a molecular link between obesity and insulin resistance (Hotamisligil, Shargill, & Spiegelman, 1993; Uysal, Wiesbrock, Marino, & Hotamisligil, 1997); TNF-α is also a macrophage-derived inflammatory factor, it alters insulin signaling in cultured cells and in vivo (Hotamisligil, 1999), and it has been reported that chronic exposure of cells or whole animals to TNF-α induces insulin resistance (Uysal et al., 1997). Regarding Hs-CRP, it has been shown to independently predict myocardial infarction, stroke, and peripheral artery disease (Zwacka, Hornbach, & Torzewski, 2001). The effects on cytokines were mild but significant; this is probably due to the fact that, first of all, the enrolled patients were not diabetic, but dysglycemic, and we have already showed that cytokines levels were higher in diabetic patients compared with not diabetic patients (Derosa et al., 2010a, 2010b). Moreover, the study duration was of only 6 months, probably to see a reduction of these parameters, longer studies are needed.

Two study limitations are the small sample enrolled and the short study duration; moreover, we did not verified if the effects recorded were maintained even after the study end.

5 | CONCLUSION

We can conclude that the administration of a nutraceutical containing polyphenolic composition as *A. nodosum* and *F. vesiculosus* can be helpful, in addition to a correct lifestyle, in improving insulin sensitivity and glycemic status, causing a regression of dysglycemia from IGT to IFG, or from IFG to NGT and an improvement of inflammation status. Of course, further larger randomized controlled studies are required to confirm the positive effects of these agents.

CONFLICT OF INTEREST

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

AUTHORS CONTRIBUTIONS

Design and conduction of the study: Giuseppe Derosa, Pamela Maffioli; data collection: all authors; data interpretation and manuscript writing: Giuseppe Derosa, Pamela Maffioli. All authors read and approved the final version of the manuscript.

ORCID

Giuseppe Derosa https://orcid.org/0000-0003-3573-4760

REFERENCES

American Diabetes Association (2014). Standards of medical care in diabetes. *Diabetes Care*, *37*, S14–S80. https://doi.org/10.2337/dc14-S014

Baldrick, F. R., McFadden, K., Ibars, M., Sung, C., Moffatt, T., Megarry, K., … Gill, C. I. R. (2018). Impact of a (poly)phenol-rich extract from the brown algae *Ascophyllum nodosum* on DNA damage and antioxidant activity in an overweight or obese population: A randomized controlled trial. *The American Journal of Clinical Nutrition*, *108*(4), 688–700. https://doi.org/10.1093/ajcn/nqy147

Bartnik, M., Norhammar, A., & Rydén, L. (2007). Hyperglycaemia and cardiovascular disease. *Journal of Internal Medicine*, *262*, 145–156. https://doi.org/10.1111/j.1365-2796.2007.01831.x

Bunn, H. F., Gabbay, K. H., & Gallop, P. M. (1978). The glycosylation of haemoglobin. Relevance to diabetes mellitus. *Science*, *200*, 21–27.

Constans, J., & Conri, C. (2006). Circulating markers of endothelial function in cardiovascular disease. *Clinica Chimica Acta*, *368*(1–2), 33–47. https://doi.org/10.1016/j.cca.2005.12.030

De Martin, S., Gabbia, D., Sirianni, A., Treglia, F., Lanna, G., Cicerchia, F., … De Martino, A. (2017). *Effect of dietary supplementation with Fucus vesiculosus and Ascophyllum nodosum (GdueTM) on fasting blood insulin and glucose levels and abdominal circumference: A clinical study*. Abstract. World Congress on November 16-18. Barcelona, Spain: Nutrition and Obesity Prevention Source.

Derosa, G., D'Angelo, A., Salvadeo, S. A., Ferrari, I., Fogari, E., Gravina, A., … Cicero, A. F. (2010a). Oral glucose tolerance test effects on endothelial inflammation markers in healthy subjects and diabetic patients. *Hormone and Metabolic Research*, *42*(1), 8–13. https://doi.org/10.1055/s-0029-1237728

Derosa, G., D'Angelo, A., Salvadeo, S. A., Ferrari, I., Fogari, E., Gravina, A., … Cicero, A. F. (2010b). Modification of vascular and inflammation biomarkers after OGTT in overweight healthy and diabetic subjects. *Microvascular Research*, *79*(2), 144–149. https://doi.org/10.1016/j.mvr.2010.01.002

Derosa, G., Ferrari, I., D'Angelo, A., Salvadeo, S. A., Fogari, E., Gravina, A., … Cicero, A. F. (2009). Oral fat load effects on inflammation and endothelial stress markers in healthy subjects. *Heart and Vessels*, *24*(3), 204–210. https://doi.org/10.1007/s00380-008-1109-y

European Diabetes Policy Group (1999). A desktop guide to type 2 diabetes mellitus. *Diabetic Medicine*, *16*, 716–730. https://doi.org/10.1046/j.1464-5491.1999.00166.x

Gabbia, D., Dall'Acqua, S., Di Gangi, I. M., Bogialli, S., Caputi, V., Albertoni, L., … De Martin, S. (2017). The phytocomplex from *Fucus vesiculosus* and *Ascophyllum nodosum* controls postprandial plasma glucose levels: An in vitro and in vivo study in a mouse model of NASH. *Marine Drugs*, *15*, 41. https://doi.org/10.3390/md15020041

Gerstein, H. C. (2010). More insights on the dysglycaemia-cardiovascular connection. *Lancet*, *375*(9733), 2195–2196. https://doi.org/10.1016/S0140-6736(10)60973-7

Heding, L. G. (1972). Determination of total serum insulin (IRI) in insulin-treated diabetic patients. *Diabetologia*, *8*, 260–266. https://doi.org/10.1007/BF01225569

Hotamisligil, G. S. (1999). The role of TNF-alpha and TNF receptors in obesity and insulin resistance. *Journal of Internal Medicine*, *245*, 621–625. https://doi.org/10.1046/j.1365-2796.1999.00490.x

Hotamisligil, G. S., Shargill, N. S., & Spiegelman, B. M. (1993). Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science*, *259*, 87–91. https://doi.org/10.1126/science.7678183

Kjaergaard, A. G., Dige, A., Krog, J., Tønnesen, E., & Wogensen, L. (2013). Soluble adhesion molecules correlate with surface expression in an in vitro model of endothelial activation. *Basic & Clinical Pharmacology & Toxicology*, *113*, 273–279. https://doi.org/10.1111/bcpt.12091

Lichtenstein, A. H., Appel, L. J., Brands, M., Carnethon, M., Daniels, S., Franch, H. A., … Wylie-Rosett, J. (2006). Summary of American Heart Association diet and lifestyle recommendations revision 2006. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *26*, 2186–2191. https://doi.org/10.1161/01.ATV.0000238352.25222.5e

Matthews, D. R., Hosker, J. P., Rudenski, A. S., Naylor, B. A., Treacher, D. F., & Turner, R. C. (1985). Homeostasis model assessment: Insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, *28*, 412–419. https://doi.org/10.1007/BF00280883

Paradis, M. E., Couture, P., & Lamarche, B. (2011). A randomised crossover placebo-controlled trial investigating the effect of brown seaweed (*Ascophyllum nodosum* and *Fucus vesiculosus*) on postchallenge plasma glucose and insulin levels in men and women. *Applied Physiology, Nutrition, and Metabolism*, *36*, 913–919. https://doi.org/10.1139/h11-115

Peter, K., Weirich, U., Nordt, T. K., Ruef, J., & Bode, C. (1999). Soluble vascular cell adhesion molecule-1 (VCAM-1) as potential marker of atherosclerosis. *Thrombosis and Haemostasis*, *82*(1), 38–43.

Rifai, N., Tracy, R. P., & Ridker, P. M. (1999). Clinical efficacy of an automated high-sensitivity C-reactive protein assay. *Clinical Chemistry*, *45*(12), 2136–2141.

Roy, M. C., Anguenot, R., Fillion, C., Beaulieu, M., Bèrubé, C., & Richard, D. (2011). Effect of a commercially-available algal phlorotannins extract on digestive enzymes and carbohydrate absorption in vivo. *Food Research International*, *44*, 3026–3029. https://doi.org/10.1016/j.foodres.2011.07.023

The Council for International Organisation of Medical Sciences. Proposed International Guidelines for Biomedical Research Involving Human Subjects. Geneva, 1982.

Uysal, K. T., Wiesbrock, S. M., Marino, M. W., & Hotamisligil, G. S. (1997). Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. *Nature*, *389*, 610–614.

Winer, B. J. (1971). *Statistical principles in experimental design* (2nd ed.). New York: McGraw-Hill.

Witkowska, A. M., & Borawska, M. H. (2004). Soluble intercellular adhesion molecule-1 (sICAM-1): An overview. *European Cytokine Network*, *15*(2), 91–98.

Zhang, M., & Tracey, K. (1988). *The cytokine handbook* (3rd ed.). San Diego, USA: Academic Press.

Zwacka, T. P., Hornbach, V., & Torzewski, J. (2001). C-reactive protein-mediated lipoprotein uptake by macrophages. *Circulation*, *103*, 1194–1197. https://doi.org/10.1161/01.CIR.103.9.1194

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