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Effects on Glyco-Metabolic Control after 12 Months of Treatment with a Supplement of Ilex Paraguariensis, White Mulberry and Chromium Picolinate in Non-Diabetic Patients with Dysglycemia

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Abstract The primary endpoint of the current study was to evaluate whether the effects previously demonstrated in the 3-month study could be maintained for 12 months. Patients were randomized to take Glicoset® in addition to a standardized diet, or to follow a standardized diet alone for 12 months. Glicoset® was self-administered once a day, 1 tablet during the breakfast. After 12 months, 31.9 % of patients retuned to a normal glycemic status in the group treated with nutraceutical + diet vs 3.3 % of patients in diet alone group ($p < 0.05$). At the end of the study 43.6% were classified as IFG in the group treated with nutraceutical + diet group vs 37% in diet alone group ($p < 0.05$). In the group treated with nutraceutical + diet, 24.5% were classified as IGT at the end of the study vs 51.1% in diet alone group ($p < 0.01$). In diet alone group, 8.7% developed type 2 diabetes mellitus vs 0 patients in diet + nutraceutical group ($p < 0.05$). Total cholesterol, LDL-C, and Tg were lower in the group treated with the nutraceutical combination. The positive effects on glycemic and lipid profile already showed in a 3 months study were also maintained after 12 months of treatment with a nutraceutical containing Ilex Paraguariensis, White Mulberry and Chromium Picolinate.

Keywords: *Ilex Paraguariensis, White Mulberry, Chromium Picolinate*

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1. Introduction

It is largely known that the failure to correct the risk factors related to the metabolic syndrome can lead, over time, to the development of important cardio-metabolic diseases, including type 2 diabetes mellitus [1]. Educating the patient to correct his lifestyle is essential to prevent the onset of these pathologies, but it is not easy, both due to the ineffectiveness of the doctor's advice and due to the patient's unwillingness to change his lifestyle [2]. In particular, in overweight or obese subjects, dysglycemia is often found. Dysglycemia is defined as a fasting glycemia ≥ 100 and < 126 mg/dl; if patient does not modify his lifestyle by correcting his diet and practicing adequate physical activity dysglycemia can evolve in type 2 diabetes mellitus. There is wide evidence in the literature that nutraceuticals can help in controlling dysglycemia in patients at risk of developing type 2 diabetes mellitus [3]. However, one of the still unsolved problems is patient compliance to treatment and the maintenance of therapy adherence on the long term: usually patient takes the nutraceutical for the first few months and then tends to be less adherent to the treatment. The reasons for this behavior are linked to inadequate medical advice, to reasons of costs that the patient has to sustain given that the nutraceutical is not reimbursed by the National Health System and to the fact that, often, it is thought that a nutraceutical may be similar to another one. In one of our previous studies, we evaluated a nutraceutical based on Ilex Paraguariensis, Morus Alba (an extract of the leaf standardized to 2% I-deoxinojirimcina), and Chromium Picolinate (Glicoset® marketed by SPA) for 3 months, showing that the nutraceutical significantly reduced fasting plasma glucose, post-prandial glucose, HOMA-IR, and glycated hemoglobin compared to baseline and to placebo ($p < 0.05$, for all) [4]. However, the persistence of

euglycemia continuing in the months following the end of the study is still under discussion. At this regard, we designed another study, lasting 12 months, where we evaluated the efficacy of the same nutraceutical in dysglycemic patients on the long term.

The primary endpoint of the current study was to evaluate whether the effects previously demonstrated in the 3-month study could be maintained for 12 months.

2. Materials and Methods

2.1. Study Design

This 12-months clinical trial was conducted at the Centre of Diabetes and Metabolic Diseases, Department of Internal Medicine and Therapeutics, University of Pavia and Fondazione IRCCS Policlinico San Matteo, PAVIA, Italy.

The study protocol was approved by institutional review board and was conducted in accordance with the 1994 Declaration of Helsinki [5], 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.

2.2. Patients

We enrolled patients with IFG or IGT, not taking hypoglycemic agents (both pharmaceuticals or nutraceutical agents). Suitable patients, identified from review of case notes and/or computerized clinic registers, were contacted by the investigators in person or by telephone.

Patients were excluded if they had type 1 or type 2 diabetes mellitus, impaired hepatic function (defined as plasma aminotransferase and/or gamma-glutamil transpeptidase level higher than the three times the upper limit of normal [ULN] for age and sex), impaired renal function (defined as serum creatinine level higher than the ULN for age and sex), or gastrointestinal disorders; current or previous evidence of ischemic heart disease, heart failure, or stroke; weight change of > 3Kg during the preceding 3 months; malignancy, and significant neurological or psychiatric disturbances, including alcohol or drug abuse. Excluded medications (within the previous 3 months) included hypoglycemic agents, laxatives, β-agonists (other than inhalers), cyproheptadine, anti-depressants, anti-serotoninergics, phenothiazines, barbiturates, oral corticosteroids, and anti-psychotics. Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded.

2.3. Treatment

Patients were randomized to take Glicoset® in addition to a standardized diet, or to follow a standardized diet alone for 12 months. Glicoset® was self-administered once a day, 1 tablet during the breakfast (Table 1). Randomisation was done using a drawing of envelopes containing randomisation 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.

Table 1. Composition of Glicoset®

Ingredients	Daily intake
ILEX PARAGUARIENSIS	1000 mg
MORUS ALBA 2% I-deoxinojirimcina	50 mg of which 1 mg DNJ
CHROMIUM PICOLINATE	100 mcg (250% RDD)
Silicon Dioxide	q.s.
Magnesium Stearate	q.s.
Dicalcium Posphate	q.s.
Microcrystalline Cellulose	q.s.

RDD: Recommended Daily Dose; DNJ: I-deoxinojirimcina; q.s: quantum sufficit.

2.4. Diet and Exercise

Patients began a controlled-energy diet (near 600 Kcal daily deficit) based on American Heart Association (AHA) recommendations that included 50% of calories from carbohydrates, 30% from fat (6% saturated), and 20% from proteins, with a maximum cholesterol content of 300 mg/day and 35 g/day of fiber. Patients were not treated with vitamins or mineral preparations during the study.

Standard diet advice was given by a dietitian and/or specialist doctor. Dietitian and/or specialist doctor periodically provided instruction on dietary intake recording procedures as part of a behaviour modification program and then later used the subject's food diaries for counselling. Individuals were also encouraged to increase their physical activity by walking briskly for 20 to 30 minutes, 3 to 5 times per week, or by cyclette. The recommended changes in physical activity throughout the study were assessed at each visit using the subject's activity diary.

2.5. Assessments

Before starting the study, all patients underwent an initial screening assessment that included a medical history, physical examination, vital signs (blood pressure and heart rate), a 12-lead electrocardiogram, measurements of height and body weight, calculation of body mass index (BMI), assessment of FPG, PPG, HbA_{1c}, fasting plasma insulin (FPI), HOMA index, TC, low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), Tg, aspartate aminotransferase (AST), alanine aminotransferase (ALT), high-sensitivity C-reactive protein (Hs-CRP).

All parameters were assessed at baseline and after 12 months since the study start. Moreover, at baseline, and after 12 months, patients underwent an oral glucose tolerance test (OGTT).

All plasmatic variables were determined after a 12-hour overnight fast, with the exception of PPG. For a description of how each parameter was assessed, please see our previous study [4].

2.5.1. Safety Measurements

Treatment tolerability was assessed at each study visit using an accurate interview of patients by the investigators, and comparisons of clinical and laboratory values with baseline levels. Safety monitoring included physical examination, vital sign assessment, weight, electrocardiogram, adverse events, and laboratory tests. Liver function was evaluated by measurement of transaminases (AST, ALT), and all adverse events were recorded.

2.6. Statistical Analysis

An intention-to-treat (ITT) analysis was conducted in patients who had received ≥1 dose of study medication and had a subsequent efficacy observation. 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 glycemia change from the end of the study did not differ significantly between diet alone and diet + Glicoset® was tested using analysis of variance and analysis of covariance (ANCOVA) models [6]. Similar analyses were applied to the other variables. The statistical significance of the independent effects of treatments on the other variables was determined using ANCOVA. A 1-sample *t* test was used to compare values obtained before and after treatment administration; 2-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 188 patients were enrolled in the trial. Of these, 96 were randomized to follow diet in addition to Glicoset®, and 92 to diet alone. One hundred and eighty-six subjects completed the study; there were 2 patients who did not complete the study and the reasons for premature withdrawal included non-compliance to treatment or lost to follow-up. The characteristics of the patient population at the study entry, and during the study, are shown in Table 2 – Table 3.

3.3.1. Anthropometric Parameters and Glycemic Metabolism

Body mass index or circumferences did not change during the study with neither treatment (Table 3).

Fasting plasma glucose, PPG, and HbA_{1c} decreased in the group treated with the nutraceutical combination in addition to diet, both compared to baseline, and compared to diet alone ($p < 0.05$, for both). HOMA-IR, but not FPI was reduced by the nutraceutical treatment, both compared to baseline ($p < 0.05$), and to diet alone ($p < 0.05$) (Table 3).

3.2. OGTT Results

At baseline, 45.8% of patients were affected by IFG in the group treated with diet + nutraceutical group vs 47.8% in diet alone group (p not significant), while 54.2% of patients were affected by IGT in the group treated with diet + nutraceutical, and 52.2% in diet alone group (p not significant). After 12 months, 31.9 % of patients retuned to a normal glycemic status in the group treated with nutraceutical + diet vs 3.3 % of patients in diet alone group ($p < 0.05$). At the end of the study 43.6% were classified as IFG in the group treated with nutraceutical + diet group vs 37% in diet alone group ($p < 0.05$). In the group treated with nutraceutical + diet, 24.5% were classified as IGT at the end of the study vs 51.1% in diet alone group ($p < 0.01$). In diet alone group, 8.7% developed type 2 diabetes mellitus vs 0 patients in diet + nutraceutical group ($p < 0.05$) (Table 2, Table 3, and Table 5, and Figure 1).

3.3. Lipid Profile

Total cholesterol, LDL-C, and Tg were lower in the group treated with the nutraceutical combination, both compared to baseline, and to diet alone group ($p < 0.05$ for both) (Table 3).

Table 2. Baseline, and 12-months data of patients during Glicoset® treatment and diet

Parameters	Diet + Glicoset®		Diet	
	Baseline	12 months	Baseline	12 months
Patients	96	94	92	92
M/F	49/47	48/46	45/47	45/47
Smoking status (M/F)	17/19	17/18	16/15	16/15
IFG (n; %)	24/20 (45.8)	10/12 (23.4)	23/21 (47.8)	15/16 (33.7)
IGT (n; %)	27/25 (54.2)	13/10 (24.5)	25/23 (52.2)	20/16 (39.1)
EU from IFG (n; %)	-	13/8 (22.3)	-	1/1 (2.2)
EU from IGT (n; %)	-	5/4 (9.6)	-	0/1 (1.1)
IFG from IGT (n: %)		9/10 (20.2)		2/1 (3.3)
IGT from IFG (n: %)	-	0/0	-	7/4 (12.0)
D from IFG (n; %)	-	0/0	-	0/0
D from IGT (n; %)	-	0/0	-	3/5 (8.7)
Lost to FU from IFG (n; %)	-	1/0 (1.1)	-	0/0
Lost to FU from IGT (n; %)	-	0/1 (1.1)	-	0/0

M: males; F: females; IFG: impaired fasting glycemia; IGT: impaired glucose tolerance; EU: euglycemia; D: diabetes.

Table 3. Baseline, and 12-months data of patients during Glicoset® treatment and diet

Parameters	Diet + Glicoset®		Diet	
	Baseline	12 months	Baseline	12 months
Patients	96	94	92	92
M/F	49/47	48/46	45/47	45/47
Age (years)	56.2 ± 7.3	-	55.8 ± 7.1	-
Smoking status (M/F)	17/19	17/18	16/15	16/15
Height (cm)	1.69 ± 0.05	1.69 ± 0.05	1.68 ± 0.04	1.68 ± 0.04
Weight (Kg)	80.4 ± 7.3	79.2 ± 7.0	81.2 ± 7.9	80.1 ± 7.2
BMI (Kg/m^2)	28.2 ± 2.6	27.7 ± 2.3	28.8 ± 2.9	28.3 ± 2.5
WC (cm)	90.7 ± 3.5	90.6 ± 3.4	90.9 ± 3.6	90.1 ± 3.3
HC (cm)	87.8 ± 2.9	87.6 ± 2.8	88.0 ± 3.0	87.5 ± 2.7
AC (cm)	99.7 ± 3.5	99.5 ± 3.3	99.8 ± 3.6	99.2 ± 3.1
FPG (mg/dl)	112.8 ± 6.9	103.2 ± 5.2*^	113.5 ± 7.1	109.6 ± 6.5
PPG (mg/dl)	136.1 ± 16.3	128.2 ± 14.1*^	132.8 ± 15.7	130.3 ± 15.1
HbA_{1c} (%)	5.9 ± 0.3	5.5 ± 0.2*^	6.0 ± 0.4	5.9 ± 0.3
FPI (μU/ml)	10.8 ± 6.1	9.7 ± 5.8	11.2 ± 7.2	11.0 ± 7.1
Homa-IR	3.1 ± 1.2	2.5 ± 0.9*^	3.1 ± 1.2	3.0 ± 1.1
TC (mg/dl)	231.6 ± 12.8	214.5 ± 10.6*^	234.2 ± 14.1	230.2 ± 13.4
LDL-C (mg/dl)	164.6 ± 15.1	150.0 ± 12.7*^	168.9 ± 16.3	166.0 ± 15.6
HDL-C (mg/dl)	41.6 ± 5.8	42.9 ± 6.4	40.4 ± 5.3	40.6 ± 5.4
Tg (mg/dl)	126.7 ± 20.2	108.1 ± 14.2*^	124.3 ± 19.8	117.9 ± 17.3
AST (UI/l)	19.4 ± 8.3	19.0 ± 8.1	19.2 ± 8.0	18.8 ± 7.9
ALT (UI/l)	23.7 ± 9.9	22.6 ± 9.5	24.6 ± 10.1	24.2 ± 10.0
Crea (mg/dl)	0.8 ± 0.03	0.8 ± 0.03	0.9 ± 0.02	0.9 ± 0.02
Hs-CRP (mg/l)	1.0 ± 0.5	0.9 ± 0.4	1.1 ± 0.7	1.1 ± 0.7

Data are expressed as mean ± standard deviation
* $p < 0.05$ vs baseline; ^ $p < 0.05$ vs Diet.
M: males; F: females; BMI: body mass index; WC: waist circumference; HC: hip circumference; AC: abdominal circumference; FPG: fasting plasma glucose; PPG: postprandial glucose; HbA_{1c}: glycated hemoglobin; FPI: fasting plasma insulin; Homa-IR: homeostatic model assessment for insulin resistance; TC: total cholesterol; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein-cholesterol; Tg: triglycerides; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Crea: creatinine; Hs-CRP: high sensitivity C-reactive protein.

Table 4. Results of the randomized patients, after OGTT at baseline

		Diet + Glicoset®		Diet	
	Time (minutes)	Glycemia (mg/dl)	Patients (n; M/F)	Glycemia (mg/dl)	Patients (n; M/F)
IFG	0	105.3 ± 5.0	44 (24/20)	108.4 ± 6.9	44 (23/21)
	120	124.2 ± 12.8		126.3 ± 12.6	
IGT	0	110.7 ± 8.1	52 (27/25)	113.7 ± 8.5	48 (25/23)
	120	168.4 ± 19.8		171.3 ± 21.4	

M: males; F: females; IFG: impaired fasting glycemia; IGT: impaired glucose tolerance.

Table 5. Results of the randomized patients, after OGTT at the end of 12 months

		Diet + Glicoset®		Diet	
	Time (minutes)	Glycemia (mg/dl)	Patients (n, M/F)	Glycemia (mg/dl)	Patients (n, M/F)
IFG	0	102.1 ± 6.4	23 (11/12)	107.1 ± 7.3	42 (22/20)
	120	120.3 ± 10.9		125.2 ± 11.5	
IGT	0	106.4 ± 8.8	43 (22/21)	110.4 ± 10.8	47 (25/22)
	120	153.5 ± 15.1		162.8 ± 23.3	

Data are means ± SD
n: number of subjects; IFG: impaired fasting glucose, IGT: impaired glucose tolerance.

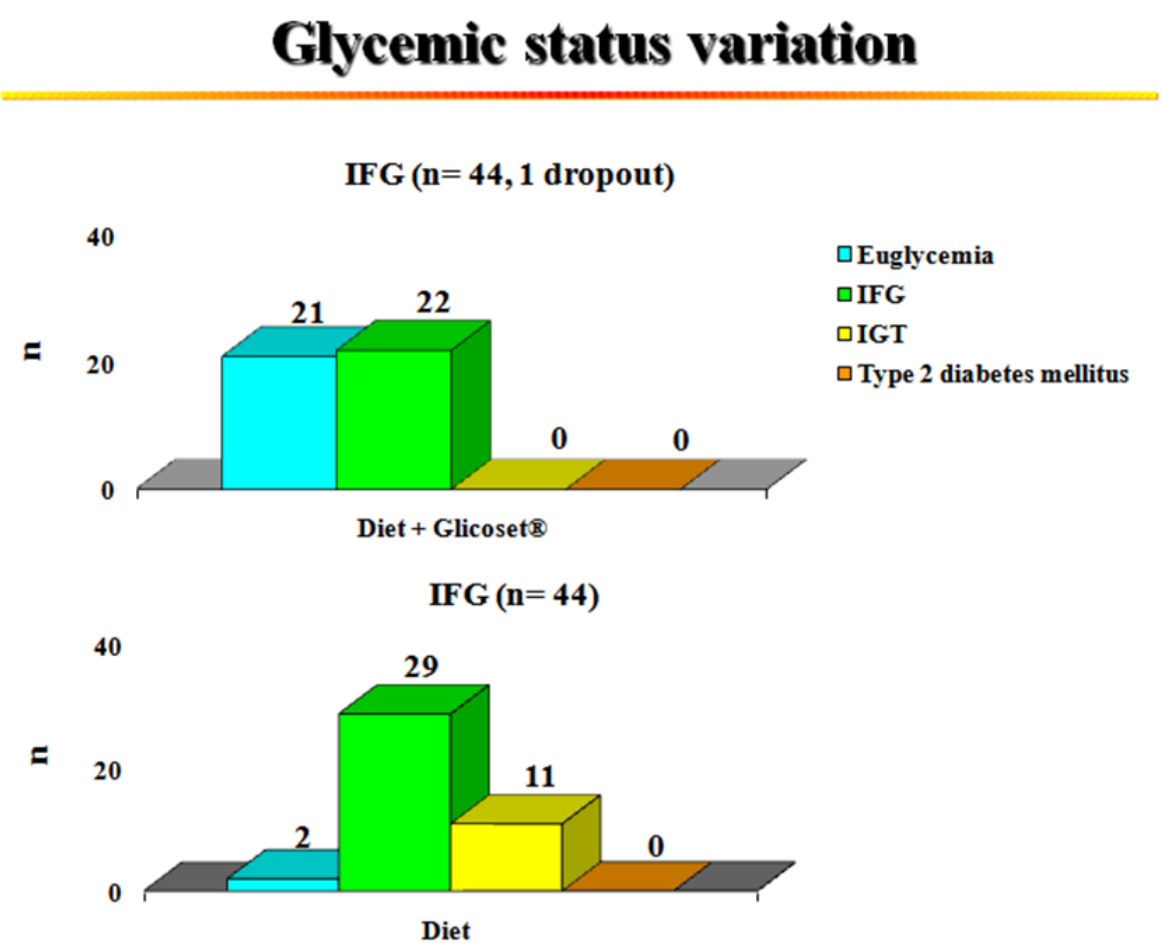

Figure 1. glycemic status variation in patients with IFG during the study (IFG: impaired fasting glucose, IGT: impaired glucose tolerance)

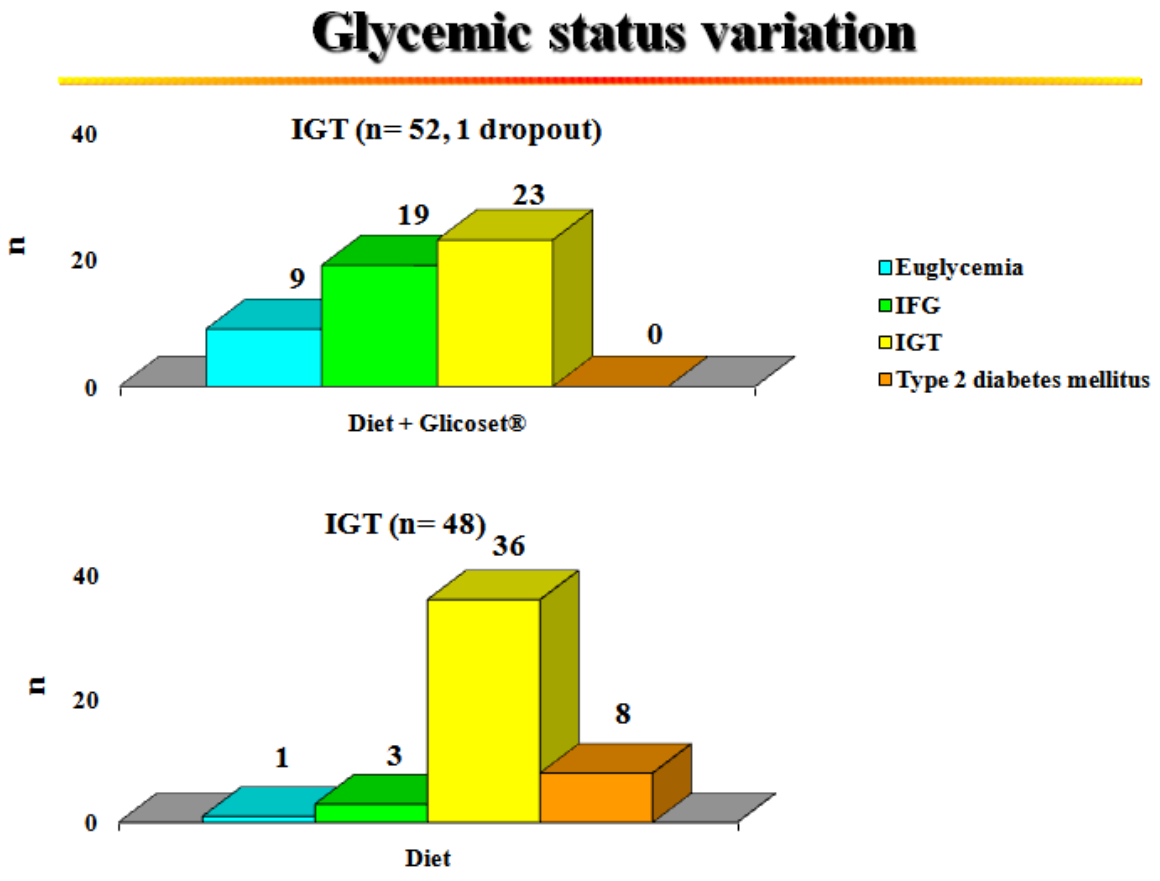

Figure 2. glycemic status variation in patients with IGT during the study (IFG: impaired fasting glucose, IGT: impaired glucose tolerance)

3.4. Cytokines

No changes in Hs-CRP were observed during the study (Table 3).

3.5. Safety and Treatment Acceptance

No significant variations of hepatic and renal function were recorded during the study. No adverse events were observed through the study period.

4. Discussion

This study demonstrated that after 12 months of therapy with Ilex Paraguariensis, Morus Alba (an extract of the leaf standardized to 2% I-deoxinojirimcina), and Chromium Picolinate (Glicoset®) the value of FPG, PPG, HbA_{1c} and of the Homa-IR were significantly improved. This confirms our previous study with the same product [5], but with a shorter observation period (3 months). We had a reduction of 8.5% in FPG, 5.8% in PPG, 6.8% in HbA_{1c} and 19.4% in Homa-IR, respectively, and no adverse events were reported. Currently, there are no studies in the literature with this nutraceutical that report these data on glucose metabolism. Our previous study lasting 18 months [7] had shown that n-3 polyunsaturated fatty acids (n-3 PUFAs) were able to reduce FPG by 5.5% and by 16.1% Homa-IR. Interestingly, we also noted the confirmation of the action on lipid metabolism of the nutraceutical under study which had already been observed in our previous three-month study. Both TC, LDL-C and Tg were significantly reduced by 7.4%, 8.9% and 14.7%, respectively. These data are partially in agreement with a previous study conducted by de Morais which demonstrated a significant reduction of 8.7% and 7.3% of LDL-C after 20 and 40 days in normolipidemics and of 8.1% and 8.6% after 20 and 40 days in dyslipidemics, respectively, but had not noticed improvements in Tg in normolipidemics (+13.2% at 20 days and -0.5% at 40 days) and in dyslipidemics (-3.2% at 20 days and -2.9% at 40 days). The subjects were defined as dyslipidemic (while our patients were hypercholesterolaemic, with normal Tg values), but the observation period of the study was decidedly shorter than ours. The same nutraceutical used consisted only of Ilex Paraguariensis and the shape was different: therefore, the comparison, although mentioned, does not seem appropriate. Therefore, also in this case we can say that the literature does not help us in the comparison.

5. Conclusions

The positive effects on glycemic and lipid profile already showed at 3 months, were also maintained after 12 months of treatment with a nutraceutical containing Ilex Paraguariensis, White Mulberry and Chromium Picolinate with a statistically significant reduction of FPG, PPG, HbA_{1c} and Homa-IR as regards glycemic metabolism and a statistical significant reduction of TC, LDL-C and Tg as regards lipid profile.

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