Original Research

Nutrafoods (2016) 15:93-99
DOI 10.17470/NF-016-1033-2

The impact of a nutraceutical on insulin resistance in patients with non-alcoholic fatty liver disease: a retrospective observational study

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Keywords:
Berberine, Tocotrienols, Chlorogenic acid, Insulin resistance, NAFLD, Nutraceutical

Abstract

Non-alcoholic fatty liver disease (NAFLD) is a hepatic disorder, but, unlike alcoholic liver disease, occurs in individuals with moderate or no alcohol consumption. Insulin resistance is considered to be one of the driving forces of NAFLD, and is found both in obese and in normal-weight subjects. However, current therapy strategies, such as administration of vitamin E or insulin sensitizers, can have variable clinical outcomes. The aim of this study was to evaluate the effect of a nutraceutical based on berberine, tocotrienols and chlorogenic acid, in combination with diet and moderate aerobic physical activity, on biochemical parameters in NAFLD patients. A total of 19 patients with ultrasound-diagnosed NAFLD, elevated aminotransferase levels, body mass index >25 kg/m^2 and <30 kg/m^2, and/or altered lipid and/or glucose levels were enrolled in this study. Those who only followed lifestyle advice (n=10) were compared with those who had also taken the nutraceutical (n=9). We observed a marked improvement in most parameters in both groups. However, reductions in plasma glucose, insulin and HOmeostatic Model Assessment of Insulin Resistance (HOMA-IR) values were significantly greater in the nutraceutical group. Consequently, the use of the nutraceutical combination might reduce insulin resistance, which is likely the first cause of NAFLD.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is a hepatic disorder, but, unlike alcoholic liver disease, is found in individuals with moderate or no alcohol consumption and often occurs together with insulin resistance and metabolic syndrome [1, 2]. Although NAFLD is generally considered a non-progressive condition, some data have highlighted the potential evolution of steatohepatitis, and in some cases the onset of progressive fibrosis or cirrhosis [1–4]. The prevalence of NAFLD in the general population is not precisely known. According to autopsy studies, it ranges from 3% in normal-weight subjects to 19% in obese individuals [3, 5]. However, the prevalence of fatty liver disease is about 20% in subjects undergoing routine ultrasound [6, 7]. Treatment strategies have two aims: to improve echographic and metabolic parameters and, closely connected to the first objective, to increase insulin sensitivity. An appropriate diet and moderate aerobic exercise have been shown to improve the anthropometric and

Received: October 23, 2015 / Accepted: December 7, 2015

biochemical parameters associated with non-alcoholic steatosis, such as hypertransaminasaemia, elevated waist circumference, hyperlipidaemia and hyperglycaemia. In the last few years, therapeutic strategies have also included the administration of medications such as insulin sensitizers, vitamin E, silybin and cholesterol-lowering drugs, but with controversial clinical outcomes [8–11].

A nutraceutical for the management of metabolic syndrome and insulin resistance has been recently marketed [12]. The product is a combination of berberine from *Berberis aristata*, tocotrienols from *Elaeis guineensis*, and chlorogenic acid from decaffeinated green coffee (*Coffea canephora*). A randomized, placebo-controlled trial has demonstrated its effectiveness in reducing HOmeostatic Model Assessment of Insulin Resistance (HOMA-IR), cholesterol and plasma triglycerides values in overweight patients with mixed hyperlipidaemia [12]. As non-alcoholic steatosis is associated with hepatic insulin resistance in most cases observed in clinical practice [13], we hypothesized that the nutraceutical could also be useful in ameliorating insulin resistance and metabolic parameters in patients with ultrasound-diagnosed NAFLD.

This study was exploratory in nature, and sought to analyze the possible impact of this nutraceutical product, in addition to diet and moderate aerobic physical activity, on NAFLD patients who have received this treatment in our ambulatory clinic.

Materials and methods

This is a retrospective observational study approved by the Ethics Committee of Verona and Rovigo (protocol number 9942). It included a group of 19 patients who presented to our clinic from May to July 2013 with ultrasound-diagnosed NAFLD, elevated aminotransferase levels, and anthropometric and metabolic alterations associated with NAFLD.

The inclusion criteria were:

- LDL cholesterol (LDL-C) >130 mg/dl
- Fasting plasma glucose (FPG) levels between 100 and 125 mg/dl
- Chronic alterations in transaminase levels (>32 U/l in the past 3 months, which is the reference cut-off value in our hospital unit).
- At least one of the following conditions:
  - Triglyceride (TG) >150 mg/dl
  - HDL cholesterol (HDL-C) <40 mg/dl (men) or <50 mg/dl (women)
  - Body mass index (BMI) >25 kg/m^2 and <30 kg/m^2.

The exclusion criteria were:

- Known causes of chronic liver disease: viral hepatitis B and C, autoimmune hepatic diseases, hemochromatosis, A1AT deficiency, drug exposure (amiodarone, corticosteroids, tamoxifen, methotrexate, high-dose oestrogens), toxic work environment, and alcohol consumption above 50 g/day (men) or 20 g/day (women);
- Recent treatment with antilipidaemic or antidiabetic drugs.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki of 1975, as revised in 2000.

All patients were advised on appropriate qualitative dietary changes (in particular limiting carbohydrates) and advised to undertake moderate aerobic physical activity (half an hour of brisk walking per day), and were examined 3 months after their first visit to evaluate changes in anthropometric and biochemical parameters. These NAFLD patients were divided into two groups. The first group (n=10) included those who only followed lifestyle advice. The second group (n=9) included those who also took the nutraceutical. The purpose of the study was explained to the patients, and they gave written informed consent for the use of their data. We then compared those who had followed the lifestyle advice alone (n=10) with those who had also taken the nutraceutical (n=9), and assessed any additional efficacy.

The following data were collected: anthropometric parameters such as BMI and waist circumference (WC), blood pressure, heart rate, detailed alcohol consumption, ultrasound parameters and biochemical parameters (glutamic oxaloacetic transaminase [GOT], glutamic pyruvic transaminase [GPT], gamma-glutamyl transferase [γGT], total and fractionated bilirubin, ferritin, albumin, serum iron, platelets, total cholesterol [TC], HDL-

C, LDL-C, TG, FPG and fasting insulin). HOMA-IR, the Hepatic Steatosis Index (HSI) and the NAFLD Fibrosis Score (NFS) were calculated.
HOMA-IR is the simplest and most commonly used method to estimate insulin resistance. It is calculated using the following formula: fasting insulin (μU/ml)×FPG (mg/dl)/405. Insulin resistance estimated by this method has been shown to correlate with estimates obtained using the euglycaemic clamp [14]. HSI is a simple index used to evaluate the severity of NAFLD using certain biochemical parameters (TG, BMI, γGT and waist circumference) [15]. The NAFLD fibrosis score is constructed from routine clinical and laboratory variables and can accurately predict the presence or absence of advanced fibrosis in NAFLD [16].

Nutraceutical characteristics

B. aristata is an erect spinous shrub, well-known in the Ayurvedic tradition. Its roots and bark are a major source of berberine and similar alkaloids. *E. guineensis* is a palm native to Africa but grown throughout the tropics. Its oil-rich fruit is a good source of tocotrienols. The green coffee beans of *C. canephora*, also called 'Robusta coffee', are rich in valuable antioxidants such as chlorogenic acid.
The nutraceutical product (Trixy®, Nathura S.p.A.) is a yellow tablet combining 500 mg berberine from *B. aristata*, 30 mg tocotrienols from *E. guineensis* and 30 mg chlorogenic acid from *C. canephora*. The product was taken once a day for 3 months.

Statistical evaluation

All baseline and 3-month data were tabulated and subjected to statistical analysis. To evaluate the efficacy of lifestyle advice and of the nutraceutical on the selected parameters, Student's t tests were used. In each group, the final values in the third month were compared to baseline. The percentage reductions in parameters were then compared between the two groups. A value of $p<0.05$ was considered significant (two-tailed significance).
Significant differences between the two groups were identified with the parametric test, were then submitted to the non-parametric Wilcoxon–Mann–Whitney's test. The level of statistical significance was set at $p<0.05$.

Results

Baseline biochemical and anthropometric parameters

Subjects with the above inclusion criteria were selected. Despite the wide standard deviation and variability of some parameters, patients who followed lifestyle advice and those who also took the nutraceutical had relatively homogeneous characteristics at baseline (Table 1).

Effect of the nutraceutical supplementation

We observed a marked improvement in most parameters in both the control and the nutraceutical group (Table 2). For the nutraceutical group, the parameters which showed a statistically significant improvement were BMI, WC, TC, LDL-C, TG, HDL-C, FPG, insulin, HOMA-IR, HSI, GOT, GPT and γGT. For the group of patients treated with lifestyle advice, the parameters that significantly improved were BMI, WC, LDL-C, FPG, insulin, HOMA-IR, HSI, GOT, GPT and γGT.

	Nutraceutical group (n= 9)		Control group (n=10)	
	Mean	SD	Mean	SD
Age (years)	53.0	9.5	44.8	10.0
Weight (kg)	80.4	13.0	88.0	7.3
BMI (kg/m^2)	26.6	2.1	28.1	1.8
WC (cm)	99.7	9.0	103.0	4.2
TC (mg/dl)	198.9	38.6[a]	203.6	53.1[a]
LDL-C (mg/dl)	147.6	38.1[a]	155.5	54.2[a]
HDL-C (mg/dl)	41.3	6.9	38.1	6.8
TG (mg/dl)	177.3	92.3[a]	161.1	49.9[a]
FPG (mg/dl)	105.8	5.5	103.8	7.3
Insulin (μU/ml)	24.6	11.5	18.6	5.5
HOMA-IR	6.4	2.8	4.8	1.7
GOT (U/l)	35.8	13.5	54.7	37.1[a]
GPT (U/l)	52.6	14.0	85.5	51.9[a]
γGT (U/l)	91.0	46.8[a]	128.1	79.4[a]
Ferritin (ng/ml)	224.1	93.6[a]	333.6	234.9[a]
HSI	39.6	3.4	41.5	3.0
NFS	1.3	0.6	0.0	1.0

[a]Values with the widest variability.
BMI body mass index, *FPG* fasting plasma glucose, *GOT* glutamic oxaloacetic transaminase, *GPT* glutamate-pyruvate transaminase, *HDL-C* HDL cholesterol, *HOMA-IR* homeostatic model assessment of insulin resistance, HSI hepatic steatosis index, *LDL-C* LDL cholesterol, *NFS* NAFLD Fibrosis Score, *Non-HDL-C* non-HDL cholesterol, *TC* total cholesterol, *WC* waist circumference

Table 1 - Baseline characteristics of the subjects assessed in the study

	Lifestyle advice+nutraceutical (n= 9)			Lifestyle advice alone (n=10)		
	Mean change	SD	*p* Value vs. baseline	Mean change	SD	*p* Value vs. baseline
Δ Weight (kg)	−3.4	1.4	<0.001	−4.6	1.8	<0.001
Δ BMI (kg/m2)	−1.1	0.4	<0.001	−1.5	0.5	<0.001
Δ WC (cm)	−4.7	2.1	<0.001	−6.7	3.2	<0.001
Δ TC (mg/dl)	−30.7	22.6	<0.05	−18.2	26.0	0.054
Δ LDL-C (mg/dl)	−36.4	25.4	<0.05	−24.8	29.6	<0.05
Δ HDL-C (mg/dl)	+5.9	7.4	<0.05	+2.2	4.5	0.156
Δ TG (mg/dl)	−46.3	60.3	<0.05	−15.0	29.7	0.145
Δ FPG (mg/dl)	−13.0	6.7	<0.001	−4.7	5.9	<0.05
Δ Insulin (μU/ml)	−13.9	8.0	<0.001	−1.6	2.1	<0.05
Δ HOMA-IR	−3.9	2.0	<0.001	−0.6	0.8	<0.05
Δ GOT (U/l)	−11.9	8.4	<0.005	−15.3	17.3	<0.05
Δ GPT (U/l)	−23.6	10.2	<0.001	−29.5	32.4	<0.05
Δ γGT (U/l)	−44.0	33.5	<0.005	−45.9	45.3	<0.05
Δ HSI	−4.1	3.5	<0.01	−2.6	3.2	<0.05

BMI body mass index, *FPG* fasting plasma glucose, *GOT* glutamic oxaloacetic transaminase, *GPT* glutamate-pyruvate transaminase, *HDL-C* HDL cholesterol, *HOMA-IR* homeostatic model assessment of insulin resistance, *HSI* hepatic steatosis index, *LDL-C* LDL cholesterol, *NFS* NAFLD Fibrosis Score, *Non-HDL-C* non-HDL cholesterol, *TC* total cholesterol, *WC* waist circumference

Table 2 - Anthropometric and biochemical parameters after lifestyle advice and nutraceutical supplementation

The reductions in TC, TG and HDL-C were statistically significant only for the nutraceutical group and not for the control group. The reduction in NAFLD fibrosis score did not reached statistical significance, probably because the treatment period was short.

After 3 months, the two groups were significantly different as regards FGP, insulin, HOMA-IR, γGT and HSI. However, these results might have been affected by the variability of some parameters at baseline. In order to reduce this bias, we compared the percentage reductions in the parameters.

According to this analysis, the parameters in the nutraceutical group which were significantly different from the control group were FGP, insulin and HOMA-IR. The non-parametric tests confirmed these results. The mean percentage of reduction for FPG, fasting insulin and HOMA-IR was 12.2±6.1%, 54.5±10.3% and 60.0±9.3%, respectively, in the nutraceutical group, and 4.4±5.4%, 8.8±10.3% and 12.6±12.1%, respectively, in the control group (Fig. 1).

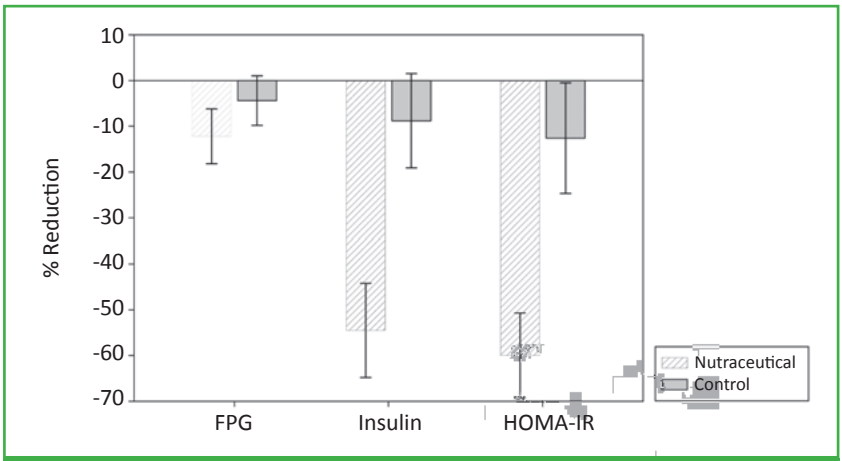

Figure 1 - Percentage reductions in fasting plasma glucose (FPG), insulin and HOMA-IR after 3 months. *FPG* fasting plasma glucose, *HOMA-IR* homeostatic model assessment of insulin resistance

Discussion and conclusions

NAFLD is the most frequent cause of transaminase elevation in asymptomatic subjects seen in clinical practice and has a multifactorial pathogenesis. However, a factor common to many forms of NAFLD seems to be insulin resistance, and NAFLD could be a strong determinant for the development of metabolic syndrome [13, 17]. Insulin resistance, which can be found both in obese and in normal-weight subjects, is related to hypertriglyceridaemia, hypertension and the visceral distribution of fat, even in the absence of obesity [13].

Excessive accumulation of liver triglycerides, due to the increased availability of free fatty acids, is, according to some authors, the so called 'first hit' of liver damage [18, 19]. A 'second hit', corresponding to oxidative stress, triggers a series of mechanisms causing hepatocellular damage, stellate cell activation, and proinflammatory cytokine production. All these events together lead to progressive chronic damage and to non-alcoholic steatohepatitis (NASH) [18, 19].

The treatment strategy for NAFLD and NASH therefore has two aims: to improve echographic and metabolic parameters and, closely connected with the first objective, to increase insulin sensi-

tivity. Hence, the following treatments have been tested in both scientific research and clinical practice: insulin sensitizers (thiazolidinediones, metformin), hypercholesterolaemic drugs (statins) and antioxidants (vitamin E, silymarin), with clinical outcomes sometimes positive but sometimes unsatisfactory. Emerging therapies for NASH include obeticholic acid, a synthetic FXR agonist bile acid [20]. However, to date no specific pharmacological treatment is recommended for long-term use in NAFLD [21].

In this study, a combination of berberine, tocotrienols and chlorogenic acid seems to have reduced some biochemical parameters – basal glycaemia and insulinaemia values, and the HOMA-IR parameter, which is representative of insulin resistance. The observed reduction in insulin resistance (60% in 3 months versus a reduction of 13% with diet only) is significant and higher than the reduction observed in the literature for berberine alone [22]. Moreover, this reduction does not seem to be dependent on weight loss, because the latter was similar in the two groups. Although we cannot definitely prove the efficacy of the product, we can suggest that the nutraceutical may have an effect on one of the main physicopathological mechanisms underlying hepatic steatosis and NASH: insulin resistance. This would be in line with observations reported in the literature regarding the mechanisms of action of the three phytocomplexes which constitute the nutraceutical.

Berberine (extracted from the bark or the root of *B. aristata*), well-known as a hypolipidaemic nutraceutical [23], improved glucose tolerance and insulin action in obese and/or diabetic mice by activating the kinase AMPK [24, 25] and reduced mitochondrial oxidative stress by acting on the uncoupling proteins (UCPs) [26]. Moreover, it increased glucose uptake in skeletal muscle cells [27]. Furthermore, berberine has been clearly demonstrated to be a useful adjunct in NAFLD both in rodents [28, 29] and in humans [30]. In many epidemiological studies, coffee intake is associated with a reduced incidence of NAFLD, NASH and diabetes, thanks to antioxidant, anti-inflammatory and antifibrotic action, and modulation of energy metabolism [31]. The evidence of a possible beneficial effect of some coffee constituents (chlorogenic acid in particular) is increasingly strong. Indeed, chlorogenic acid has been demonstrated to modulate lipidic and glucidic metabolism, even in interventional studies [32]. Tocotrienols belong to the well-known family of vitamin E compounds. However, they have a higher antioxidant potential than tocopherols, although their efficacy in NAFLD has not yet been demonstrated. Unlike tocopherols, in animal models and clinical trials tocotrienols have been shown to be effective in reducing plasma cholesterol and triglyceride levels [33].

In our study, diet modification and undertaking moderate and consistent physical activity were the first measures adopted in order to improve insulin resistance in subjects with NAFLD. Indeed, the improvement in anthropometric and in some biochemical parameters (with the exception of TC, HDL-C and TG) were significant for both the group which only followed lifestyle advice, and that which also took the nutraceutical. Transaminase values were also significantly reduced in both groups, but normalized after 3 months only in the nutraceutical group (32 U/l being the reference cut-off value in our hospital unit).

This study has many limitations. First of all, it is a retrospective observational study. In order to validate our finding it would be necessary to conduct a well-designed interventional trial. Moreover, the study has a relatively small sample size and includes patients with some heterogeneous baseline characteristics. Consequently, this study does not allow any conclusions to be drawn about the efficacy of the product regarding metabolic parameters in NAFLD patients. However, our data do indicate a treatment-related effect, whose magnitude has to be established.

In conclusion, physical activity and BMI reduction through diet modification should be the first measures adopted in order to improve insulin resistance in subjects with NAFLD. In addition, this study suggests that the administration of a nutraceutical product containing berberine, tocotrienols and chlorogenic acid may have an impact in reducing the HOMA-IR index and therefore insulin resistance, which is likely to be a first cause of NAFLD. A well-designed intervention trial is needed to validate this finding and to assess the

efficacy of the product as a natural supplement for non-alcoholic fatty liver disease.

Conflict of Interest

The authors declare that they have no conflict of interest

Consent

Informed consent was obtained from all patients for inclusion in the study

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