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Siliphos Selenium Methionine Alpha Lipoic Acid for Non Alcoholic Fatty Liver Disease: Results of a Pilot Study

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Abstract

Siliphos-selenium-methionine-alpha lipoic acid (SSMAL) has been used to treat chronic hepatic diseases, although formal evaluation of this mixture with clinical trials is lacking. We conduct this pilot study to investigate the safety and effectiveness of SSMAL in patients with non-alcoholic fatty liver disease (NAFLD). Forty NAFLD patients were randomized into two groups. All patients received metformin 1500 mg q.a.d. added to nutritional and exercise advice. Twenty patients received selenium (15 mcg) – methionine (3 mg)-alpha lipoic acid (200 mg) group. After 24 weeks, basal versus final biochemical and image studies were compared. Patients from SSMAL group, had a decrease in steatosis graded by ultrasound 70% vs. 15% ($p<0.001$) and showed lower rates of liver enzymes than control group. Pro-inflammatory cytokines profile and the reduced antioxidant status noted in NAFLD patients showed improvement with this therapy. Adiponectin was significantly increased in both groups and it changed with active therapy. No serious adverse reactions were reported. This is the first study to systematically assess SSMAL in NAFLD patients. Treatment for 6 months may protect against worsening steatosis and improve the inflammatory profile. These findings warrant further investigation. (NTC01650181)

Keywords: Siliphos; Selenium; Methionine; Alpha lipoic acid; NAFLD; Treatment

Introduction

Hepatic diseases and, particularly non-alcoholic fatty liver disease (NAFLD) have become a significant worldwide public health issue [1]. NAFLD is a condition that ranges from single fat accumulation in the liver (steatosis) and hepatic inflammation (steatohepatitis), fibrosis, cirrhosis and even hepatic cancer. Insulin resistance, oxidative stress, and inflammatory cascade may play a role in the pathogenesis and progression of fatty liver [2].

Selenium-methionine-alpha lipoic acid (SSMAL) theoretically has a powerful anti- oxidant activity [3]. It has been proposed that SSMAL may inhibit lipid peroxidation in the hepatocyte, decreases the damage caused by hydroxyethyl radicals formed in the microsomes [4]; increases protein synthesis in the hepatocyte and also, induces the reuptake of low molecular weight antioxidants, facilitating cellular regeneration [5]. SSMAL has been used in the treatment of chronic hepatic diseases, including NAFLD. The rationality behind its use in the treatment of NAFLD is its antioxidant activity and virtually non-existent side effects. Nevertheless, to date, no clinical trials have been evaluated to see SSMAL efficacy and safety in the treatment of NAFLD

We conducted the Siliphos-selenium-methionine-alpha lipoic acid Intervention Trial, a 24-week, randomized, conventional treatment controlled, exploratory trial, to evaluate the efficacy and safety of this combination in the treatment of NAFLD.

Methods

This was a pilot study, non- stratified, with balanced randomisation [1:1], one center, double-blind, standard therapy-controlled, conducted in patients attending the NAFLD clinic at the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran in Mexico City from march 2013 to july 2014.

Patients were randomly assigned to one of two parallel groups, initially in 1:1 ratio, to receiveeither one of two regimens, an independent Data Monitoring Committee reviewed unblinded data for patient safety; no interim analyses for efficacy or futility were done. Eligible participants were all adults aged 18 or over, both gender who met the eligibility criteria for according to the NAFLD guidelines [6,7] (NAFLD biopsy proven and ultrasonography images), Nonalcoholic steatohepatitis (NASH) was defined by the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis [7]. All subjects not only were prediabetic (pDM) patients (carbohydrate intolerant, impaired fasted glucose) [8] but also fulfilled the criteria for metabolic Syndrome [8] (Elevated waist circumference: >80 cm for women and >94 cm for men; Dyslipidemia, reduced HDL-C: <40 mg/dL in males; <50 mg/dL in females; Elevated blood pressure: Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg and Elevated fasting glucose ≥ 100 mg/dL). Two standardized and blinded radiologists evaluated the images (kappa 86) and two standardized and blinded pathologists evaluated the basal biopsies (kappa 82).

We excluded all patients with significant alcohol consumption, coexisting causes for chronic liver disease or steatosis and if they had received multivitamins within a 3 month period before inclusion or had a history of allergy to the excipients used in the study.

Patients were randomly assigned to receive a custom made and orally administered selenium 15 mcg-methionine 3mg-alpha lipoic acid 200 mg (SSMAL) and metformin 1500 mg q.a.d. added to nutritional and exercise advice. The control group received

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metformin 1500 mg q.a.d. added to nutritional and exercise advice. Because no treatment can be considered the gold standard in NAFLD, patients in the control and intervention groups received usual care. We decided not to use a placebo because this was a pilot study and, to our knowledge, no placebo for NAFLD has achieved success. Both groups received treatment for 24 weeks. Patients received each drug dose 30 minutes before meals.

We used www.randomization.com in order to assign participants to each arm. During data collection researchers did not have access to the randomization codes or statistical summaries of follow-up data. Patients were clinically evaluated at baseline and 4, 8, 12, 16, 20 and 24 weeks, basal versus final biochemical and image studies were compared.

The primary endpoint evaluates the efficacy and safety of this combination in the treatment of NAFLD. We evaluated the proportion of patients achieving at least 1 grade improvement in steatosis degree from baseline to 24 weeks as measured by ecosonographyc score. Additional analysis was done using liver function tests and a biochemical profile.

The sample that was studied was chosen according to consecutive cases

The ethical institutional review board approved the study (REF 399) and it was registered in clinical trials.gov (NTC01650181). All patients participating in the study gave written informed consent.

Adverse events

Adverse events were assessed at each study visit and followed until resolution. Safety monitoring included complete blood counts measurement of serum aspartate aminotransferase, alanine aminotransferase, glucose, creatinine, and partial thromboplastin time. Specific cardiovascular monitoring for adverse events was not done.

Statistical analysis

This was a pilot study with an intention-to-treat analysis, categorical variables were described with rates and percentages, continuous variables with medians and percentiles 25 and 75, according to the statistical distribution, an univariate and bivariate analysis was carried out with U Mann Whitney for median comparison, and a Wilcoxon-Mc Nemar test for continuous, or categorical variables, accordingly; for categorical variables, the Xi test and the Fisher exact test were carried out, and a percentage analysis regarding the change of biased or statistically significant variables was used. The significance level <0.05 was taken into consideration. The statistics software SPSS v20 was used (Figure 1).

Results

Forty patients were included in the study, there were 20 patients per study arm, distributed as follows: 14 women (70%) to the control group, and 12 women (60%) to the experimental group; the median age was 49.5 and 44, respectively. The overall baseline demographic and clinical characteristics for each group are presented in Table 1.

Forty patients completed the treatment regimen and all received a 6-month follow-up. Baseline parameters related to biochemical profiles are presented in Table 2.

A clinical and statistical improvement in the steatosis degree under treatment with siliphos-selenium-methionine-alpha lipoic acid ($p<0.001$) was observed (Figure 2)

Patients randomized to SSMAL group, had a clinical and statistical decrease in steatosis graded by ultrasound ($p < 0.001$). We evaluated the proportion of patients achieving at least 1 grade improvement in steatosis degree from baseline to 24 weeks as measured by ecosonographyc score between groups, 70% in SSMAL group vs 15% in standard therapy ($p < 0.001$).

We observed favorable changes in the serum levels of ALT ($p <0.001$), AST ($p < 0.001$), GGT ($p<0.001$), Ferritin ($p<0.001$) and glucose ($p<0.008$) in the treatment group (Table 3).

Regarding the determination of oxidation markers and adipocitokines, behavior is presented in Table 4, emphasizing a higher decrease of leptin levels, as well as a higher increase of adiponectin in experimental group.

Due to ethical implications, no subsequent hepatic biopsies have been performed. There were no losses in the follow up, no serious adverse effects were documented from the all of the patients under active therapy: Two patients had self-limited rashes and exanthema with a duration of less than 24 hours, two reported non-disabling nauseas, and the others did not report any adverse reactions. None of the twenty patients under standard therapy documented or reported any adverse events or reactions. From the patients who reported adverse reactions, none of them required hospital or emergency care to control symptoms; none of the adverse effects limited the Administration of doses and the 20 patients in the active therapy group completed the 6 months of treatment.

Discussion and Conclusion

Outcomes of this study suggest that the SSMAL could be a promising therapy for patients with NAFLD in the specific subgroup of Pre-Diabetes in which the benefits of metformin are indisputable. In our patients, it was possible to document a clinical and statistical improvement of aminotransferases, ferritin, GGT, glucose, the inflammatory profile (leptine/adipinectine), and malondialdehyde added to a remarkable echosonographic improvement after 6 months of treatment with SSMAL.

The fatty liver disease is an abstract disease concept that incorporates a pathology spectrum, with no effective therapies to date [9,10]. Gradual and sustained weight loss is the only measurement that has been reproducible in various studies as a therapy to improve steatosis [11]; however, quick weight loss or malnutrition may precipitate or worsen NAFLD [12]. In literature there are studies with

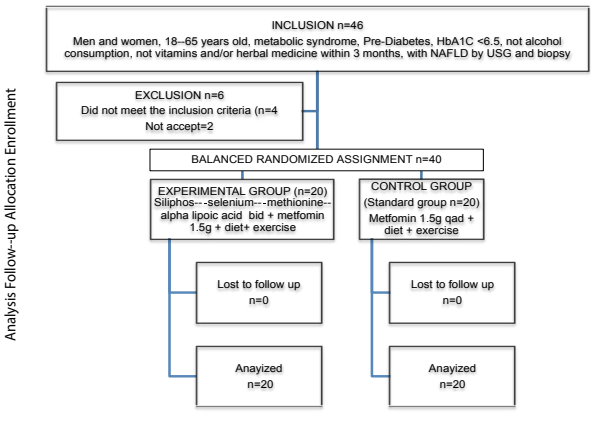
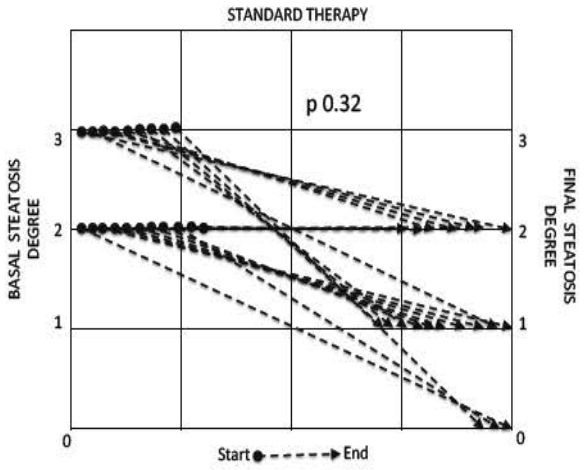


Figure 1: Flow diagram of progress through the phases.



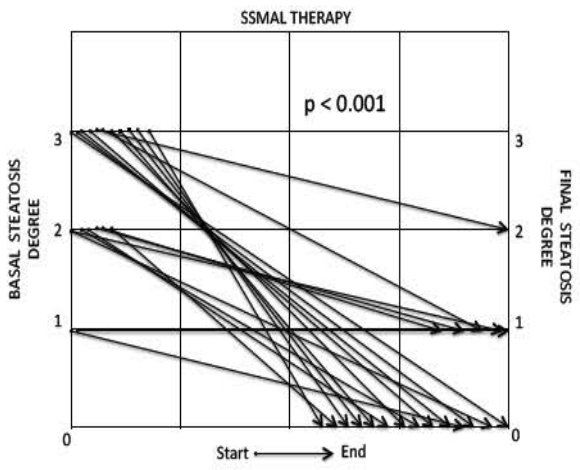


Figure 2: Echosonographic steatosis improvement according to study arm

	Standard therapy (metformin+diet+exercise)n=20	Silphos-selenium-methionine – alphalipoic acid-standard therapy n=20	Statistical significance P <0.05*
Age(years)	49.5(41.25-53.75)	44(36.7-54)	0.50
Gender (Female)	14(70%)	12(60%)	0.32
Metabolic syndrome			
Pre-Diabetes	20(100%)	20(100%)	0.59
Dyslipdemia	5 (25%)	3(15%)	0.69
Hypertension	6 (30%)	6 (30%)	0.23
Baseline steatosis Degree (Echosonography)			
Mild	0	2(10%)	
Moderate	11(55%)	7(35%)	0.14
serious	9(45%)	11 (55%)	0.11
NAFLD Hepatic Biopsy			
Steatosis	10 (50%)	10(50%)	

Data expressed as medians (MD) and percentiles (P25-75) or rates and Percentage %

Table 1: Demographic and clinical characteristics

	Standard therapy (metformin+diet+exercise) n=20	Silphos-selenium-methionine – alphalipoic acid-standard therapy n=20	Statistical significance P <0.05*
Malondiadehide Ng/dl	0.46(.20-.81)	0.51(.40-.75)	0.56
Leptin ng/ml	7.95(4.46-11.57)	6.9(2.02-10.64)	0.31
Adiponectin Mcg/ml	12358.98 (6187.85-20019.46	11516.60 (7795.92-21880.32	0.85
ALT UI	68.5 (48-99.5)	65.5(39.2-96)	0.56
AST UI	48 (29.5-73.25)	49.5 (29.75-66)	0.85
GGT UI	55.5(39-155.5)	75(39.5-144.5)	0.51
Ferritin Ng/ml	139.10(94-184.2)	150.50(93.2-299.2)	0.81
Glucose mg/dl	98(91-104)	95.5(86.5-104)	0.43
Glycosylated hemoglobin %	5.7 (5.2-6.1)	5.4(5.1-5.8)	0.18

Data expressed as medians (MD) and percentiles (P 25-75)

Table 2: Oxidation and inflammation baseline profiles

diverse antioxidants such as betaine [13], sylimarin [14,15], alpha-lipoecoic [16,17], ascorbic acid [16] and selenium [17-20]. Insulin sensitizers such as metformin and thiazolidinediones [21], have shown to normalize aminotransferases [22] but international guidelines [7] do not recommend the use of metformin as a therapy for NAFLD anymore. However, developing countries shall try to acquire all the possible evidence they can pointing out the opposing criteria given the usefulness of the drug related to the components of the metabolic syndrome. Unfortunately, and due to the lack of appropriate therapeutic modalities and solid prospective studies, addressing the treatment for NAFLD leaves open a possibility of new offers of treatment based on solid evidence.

Although the sample size represents a limitation to reach more solid inferences, the reproducibility of achievements from previous studies may drive insistence on the topic with more powerful studies. In this study, the ratio of improvement of the severity of the hepatic steatosis may be inferred not only by improvement in body composition but also mediated by molecular based mechanisms as the improvement in the inflammation and lipoperoxidation profile in those who undergo active therapy. Although measurements in studies of this kind are not exempt from bias, the authors, measured the change percentages for significant variants and put them under statistical analysis, pointing out that the statistical significance is consistently kept for AST, GGT and ferritin, together with that is evinced in the adipocytokines and lipoperoxidation profiles, the latter being included in the analysis due to the biological importance of the pathologic entity under study, as detailed in Table 5.

The main limitations of the study are: that it was a study without placebo and without a final histological assessment. The main limitation of the statistical analysis is related to the sample size and to the feasibility of a multivariate analysis.

The siliphos alpha lipoic acid and selenium methionine combination has appropriate theoretical and scientific bases for a synergistic activity that is also complementary in the antioxidant activity to hepatic level in pre-Diabetes patients under metformin treatment. Our study suggests that this novel combination is safe and well tolerated and can be added to standard therapy in patients with pDM; it improves or normalizes the aminotransferase, GGT, ferritin and glucose levels with 6 months of treatment; this added to the marked improvement in steatosis assessed by echosonography. Based on the observed with malondealdehyde, adiponectin and leptin we can infer that the steatosis degree improvement is related to the improvement in the inflammation and lipoperoxidation profile that eventually may

	Standard therapy (metformin+diet+exercise) N=20	**Siliphos-selenium-methionine-alpha lipoic acid+ standard therapy N=20**	**Statistical significance P<0.05***
ALT UI	52.50 (32.5-88.25)	35.50 (33-57.5)	<0.001
AST UI	30(24.1-40.3)	25(23.2-31.5)	<0.05
GGT UI	55(35.5-132.5)	40.5(30-73.75)	<0.001
Ferritin Ng/ml	131 (112-184.2)	101(71.5-174.75)	<0.001
Glucose mg/dl	96(87.7-98.5)	88.5(80-98)	<0.05

Data expressed as medians (MD) and percentiles (P 25-75)

Table 3: Biochemical final characteristics comparison

Standard therapy (metformin +diet +exercise) N=20		**Siliphos- selenium-methionine- alpha lipoic acid +standard therapy N=20**	**Statistical significance P<0.05***
Malondialdehyde (MDA)			
ng/dl	0.65(.53-.80)	0.41(.34-.68)	**0.040**
Leptin			
ng /ml	9.54(4.46-15.13)	5.6(1.79-9.85)	**0.034**
Adiponectin			
mcg/ml	10622.20(7319.78-19154.04)	12944.10(9687.56-20501.88)	**0.049**

Data expressed as medians (MD) and percentiles (P 25-75)

Table 4: Oxidation and inflammation final profiles comparison

	Standard therapy (metformin+diet+exercise) N=20	**Siliphos-selenium-methionine-alpha lipoic acid+ standard therapy N=20**	**Statistical significance P<0.05***
ALT UI	-28.01 (-49.7,-12.5)	-29.01(-47.1,-8.2)	0.74
AST UI	-19.75(-52.5,-15.5)	-33.80(-49.8,-15)	0.04
GGT UI	-6.4(-14,5.7)	-23.2(-30.6,-23.3)	0.004*
Ferritin ng/ml	-1.0(-8.3,2.9)	-18.7(-40.13,7.1)	0.003*
Glucose mg/dl	-1.5(-8.7,7.3)	-7.5(-12.5,-1.6)	0.06
Leptin ng/ml	-0.10(-18.2,12.7)	-13.8(-40.6,2.8)	0.03
Adiponectin mcg/ml	3.3(-26,31.2)	17.7(3.9,35.9)	0.04

Data expressed as medians (MD) and percentiles (P 25-75)

Table 5: Final change percentage for significant variables, according to the study arm

revert the cascade of necroinflammatory damage. Based on the results of this study, we deem it necessary to conduct randomized and placebo-controlled clinical studies to be able to establish its actual efficacy and demonstrate if the theoretical properties turn out to be a good available option for the treatment of fatty liver.

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