

Viusid, a nutritional supplement, in combination with diet and exercise as initial strategy of treatment in patients with non-alcoholic steatohepatitis.

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Background

Non-alcoholic fatty liver disease is currently the most common cause of elevated liver enzymes in clinical practice. Several pharmacological therapeutic options have been evaluated. However, the majority of the available studies do not have adequate statistical power or reliable end-points that allow reaching conclusions useful in clinical practice. Currently, weight reduction based on diet and exercise strategies is the basis of treatment. The lipid peroxidation and overabundance of ROS are key mediators in the progression from simple steatosis to NASH. This provides a rationale for studies using antioxidants and cytoprotective agents in therapeutic trials. Viusid is a nutritional supplement (Catalysis laboratories, Spain) with antioxidant or hepatoprotective properties that in combination with hypocaloric diet and exercise could improve the histologic features in patients with NASH

Ingredients of Viusid			
Malic acid	0.666 g	Ascorbic acid	0.020 g
Glycyrrhizic acid	0.033 g	Folic acid	66 mcg
Glucosamine	0.666 g	Cyanocobalamin	0.3 mcg
Arginine	0.666 g	Zinc sulfate	0.005 g
Glycine	0.333 g	Pyridoxal	0.6 mg
Calcium pantothenate	0.002 g		

Aim

To evaluate the efficacy and safety of Viusid, a nutritional supplement, in association with hypocaloric diet and exercise in patients with non-alcoholic steatohepatitis

Methods

Study design

Study type: Interventional

Allocation: Randomized Controlled Trial

Masking: Double blind

Experimental group: Viusid, hypocaloric diet and exercise

Control group: Hypocaloric diet, exercise and placebo

Assignment: Parallel

Endpoint: Safety/efficacy

Primary outcomes measures:

- Histological improvements: defined as improvement in liver histology as assessed by the modified Kleiner's criteria at 24 weeks (end of the treatment) "Figure 1"

Secondary outcomes measures:

- Biochemical improvements: defined as improvement in aminotransferase levels at 24 weeks (end of the treatment)
- Metabolic improvements: defined as improvement in insulin resistance at 24 weeks (end of the treatment)
- Anthropometric improvements: defined as improvement in weight and waist at 24 weeks (end of the treatment)

Subjects

Eligibility criteria

Inclusion criteria:

- Histological diagnosis of NASH
- Age between 18 and 70 years
- Ability to provide informed consent
- Absence of significant alcohol intake (weekly ethanol consumption of less than 40 g)

Exclusion criteria:

- Presence of other form of liver diseases
- Pregnancy or lactation
- Decompensated cirrhosis
- Presence of secondary causes of NAFLD
- Pharmacological treatment with some potential benefit on NAFLD
- Fasting glucose levels greater than 250 mg/dl (13.3 mmol/l)
- Contraindication to liver biopsy
- Refusal to participate in the study
- Concomitant disease with reduced life expectancy
- Severe psychiatric conditions
- Drug dependence

Treatment and assessment are summarized in figure 2

Statistical analysis

- For all laboratory measures and continuous demographics and anthropometric: P value Wilcoxon signed ranks test and proportions: percentage, P value chi-square.
- Multiple logistic regression was used to identified baseline (age and sex) and on-treatment (ALT, AST, cholesterol, triglycerides, HDL, uric acid, fasting glucose, HOMA-IR, waist, weight and adherence to treatment) factors predictive of an histological improvement in at least 4 points at the modified Kleiner's score from baseline.
- Intention to treat analysis was performed

Results

- ▶ We randomly assigned 60 patients with NASH to 6 month of treatment with a hypocaloric diet (a reduction of 620 kcal per day to the calculated daily intake required to maintain body weight) plus aerobic exercise during 40 minutes daily and Viusid 3 sachets daily or hypocaloric diet, exercise and placebo. (Figure 2)
- ▶ Paired liver biopsy was performed in 76% of the enrolled patients
- ▶ Demographic and baseline characteristic were comparable between the two groups (Table 1)
- ▶ The anthropometric, biochemical and metabolic variables were significantly improved in the two interventional groups, however, the triglycerides and uric acid concentrations were markedly reduced in those patients treated with Viusid, as compared with placebo (Table 2)
- ▶ Administration of Viusid, hypocaloric diet and exercise, as compare with placebo, was associated with improvement in histologic findings with regards to steatosis (P<0.001), ballooning (P=0.002), lobular inflammation (P=0.02), combined inflammation (P=0.003) and total score (P=0.004), but the reduction in fibrosis did not differ significantly from that in the placebo group (Table 3)
- ▶ There was a significantly correlation between loss weight in percentage and waist, and change in histological score (Figure 3 and 4)
- ▶ A comprehensive lifestyle modification based on hypocaloric diet and exercise was found to induce a loss of approximately 10% of initial weight and it was associated with marked reduction in total histological score
- ▶ Compliance with the study schedule (diet/exercise/Viusid) was 90% or greater
- ▶ Nauseas and diarrhea was reported in one subject who received Viusid. No laboratory adverse event was associated with the use of Viusid
- ▶ The multiple logistic regression analysis revealed that the normal values of HOMA-IR <2 (OR:0.18, 95% CI: 0.05-0.69, P=0.012) and ALT at the end of the study (OR: 0.21, 95% CI: 0.05-0.80, P=0.023), and treatment with Viusid (OR: 0.09, 95% CI: 0.01-0.93, P=0.043) were independently associated to histological improvement

Figure 1. Histological assesment (Adapted of Kleiner's criteria. Hepatology 2005)

Steatosis			
0	<5% of parenchyma involved	}	Total score: 11
1	5-33% parenchyma involved		
2	34-66% parenchyma involved		
3	>66% parenchyma involved		
Ballooning			
0	None	}	Total score: 11
1	Few balloon cells		
2	Many balloon cells		
Lobular inflammation			
0	0 or 1 focus	}	Total score: 11
1	2-4 foci per 200x field		
2	>4 foci per 200x field		
Fibrosis			
0	None	}	Total score: 11
1	Sinusoidal or periportal		
2	Sinusoidal and periportal or periportal		
3	Bridging fibrosis		
4	Cirrhosis		

Table 1. Baseline characteristics

Variable	Viusid, diet and exercise (n=30)	Diet, exercise and placebo (n=30)	P value
Age (yr)	45±10	49±10	0.13
Sex, n (%)			
Male	18 (60%)	16 (53%)	0.79
Female	12 (40%)	14 (47%)	
Weight (kg)	83.3±15.6	82.4±14	0.71
Body mass index (kg/m ²)	29.8±4.6	31.6±4.7	0.14
Waist (inches)	39.3±4	40.6±3.4	0.14
ALT (IU/l)	44.7±31	44±28	0.92
AST (IU/l)	36.3±27	42.5±23	0.30
Fasting plasma glucose (mmol/l)	4.8±1	4.8±1	0.81
Cholesterol (mmol/l)	5.1±1	5.3±1.3	0.66
Triglycerides (mmol/l)	2.1±1.5	1.9±0.9	0.54
HDL-C (mmol/l)	0.83±0.6	0.76±0.3	0.34
Uric acid (mmol/l)	336±94	348±83	0.36
Fasting plasma insulin (µU/ml)	17.6±6	21.5±9	0.18
Insulin sensitivity HOMA (%S)	3.8±1.2	4.3±1.3	0.25

Plus-minus values are means±SD.

For all laboratory measures and continuous demographics and anthropometric: P value Wilcoxon signed ranks test. Proportions: percentage, P value chi-square.

Figure 2. Treatment and assesment

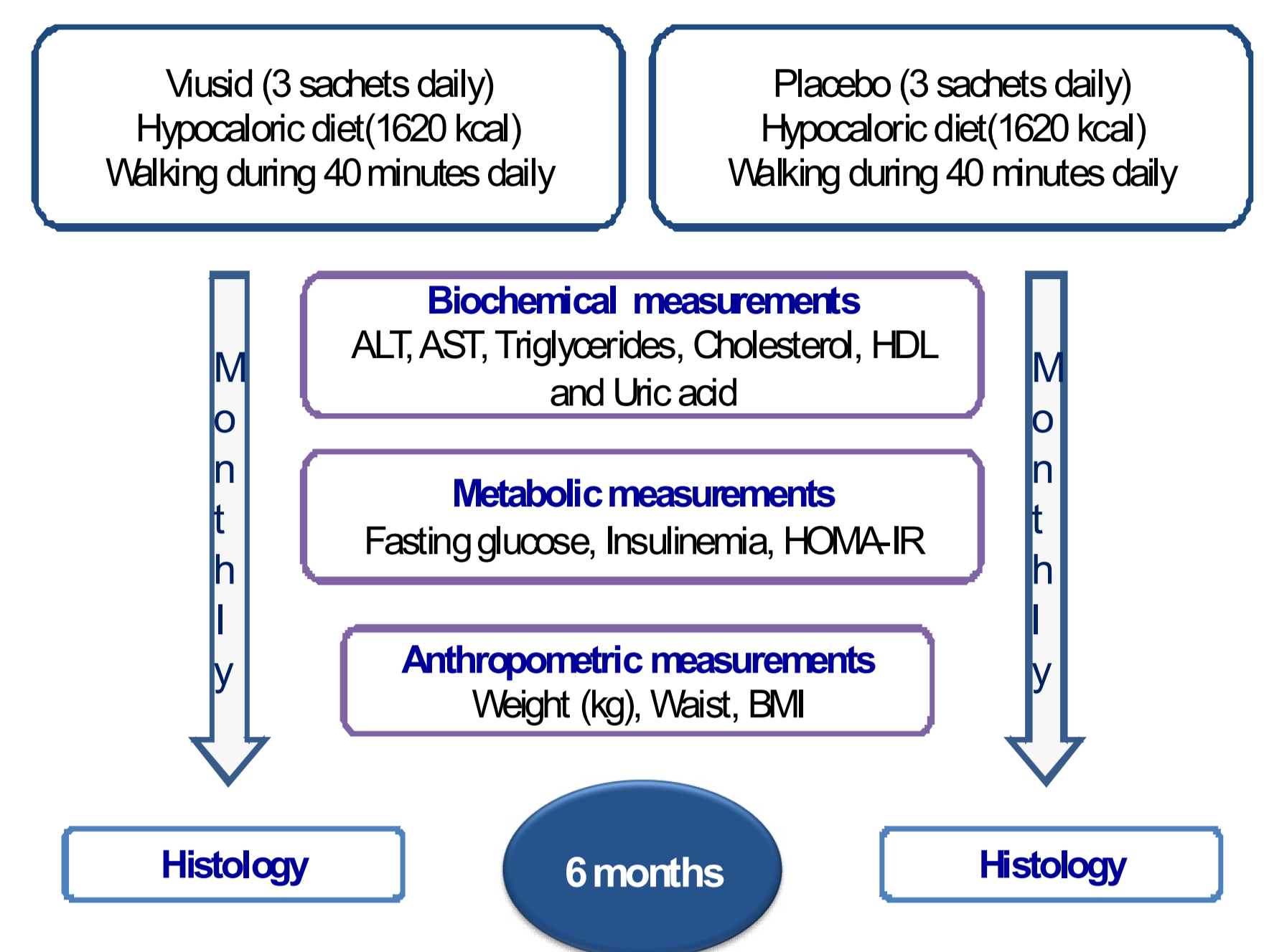


Table 2. Baseline characteristics of the patients and outcome at 6 months.

Variable	Viusid-Diet-Exercise n=30			Placebo-Diet-Exercise n=30			P value
	Before Treatment	After Treatment	P value	Before Treatment	After Treatment	P value	
Weight (kg)	83.5±15	73.6±14	<0.001	82.4±13	73.7±11	<0.001	
Waist (inches)	39.1±4	35±4.2	<0.001	40.5±3.2	36±5	<0.001	
Body mass index (kg/m ²)	29.8±5	26.3±4.8	<0.001	31.5±4	28±4.1	<0.001	
ALT (IU/l)	43±28	23±17	<0.001	46±29	27±17	0.01	
AST (IU/l)	37±23	24±14	0.02	44±23	23±12	<0.001	
Uric acid (mmol/l)	325±110	286±96	0.04	348±85	328±106	0.38	
Fasting plasma glucose (mmol/l)	4.7±0.9	4.6±0.9	0.95	4.9±0.9	5.2±1.7	0.28	
Cholesterol (mmol/l)	5.2±1	4.5±1.1	0.01	5.3±1.7	4.5±1	0.02	
Triglycerides (mmol/l)	1.9±0.8	1.3±0.5	0.01	1.8±0.9	1.9±1	0.71	
HDL-C (mmol/l)	0.84±0.2	0.85±0.2	0.86	0.70±0.3	0.70±0.3	0.86	
Fasting plasma insulin (µU/ml)	18±12	13±7	0.01	21.6±15	12.7±7	0.01	
Insulin sensitivity HOMA (%S)	3.6±2	2.1±1.2	0.01	4.3±3	3.1±2	0.01	

Plus-minus values are means±SD.

For all laboratory measures and continuous anthropometric: P value Wilcoxon signed ranks test.

Table 4. Histological characteristics of the patients and outcome at 6 months.

Variable	Viusid-Diet-Exercise n=30				Placebo-Diet-Exercise n=30				P Value for Between-Group Comparison
	Before Treatment	After Treatment	Change	P value	Before Treatment	After Treatment	Change	P value	
	Steatosis	2.27±0.6	0.4±0.2	-1.87±0.9	<0.001	2.35±0.6	1.4±0.7	-0.95±0.7	
Ballooning	0.91±0.5	0.09±0.01	-0.82±0.7	<0.001	0.95±0.5	0.40±0.2	-0.55±0.5	0.002	0.002
Lobular inflammation	1±0.6	0.05±0.01	-0.95±0.6	<0.001	1.15±0.5	0.40±0.2	-0.75±0.6	0.003	0.02
Combined inflammation	1.91±0.8	0.14±0.09	-1.77±1.2	<0.001	2.10±0.9	0.80±0.4	-1.3±0.9	<0.001	0.003
Fibrosis	0.95±0.3	0.23±0.01	-0.72±0.4	0.012	1±0.7	0.45±0.2	-0.55±0.3	0.012	0.25
Total score	4.78±1.9	0.89±0.4	-3.89±2.1	<0.001	4.95±2.6	2.64±1.9	-2.31±1.9	<0.001	0.004

Figure 3. Correlation between loss weight in percentage and change in histological score

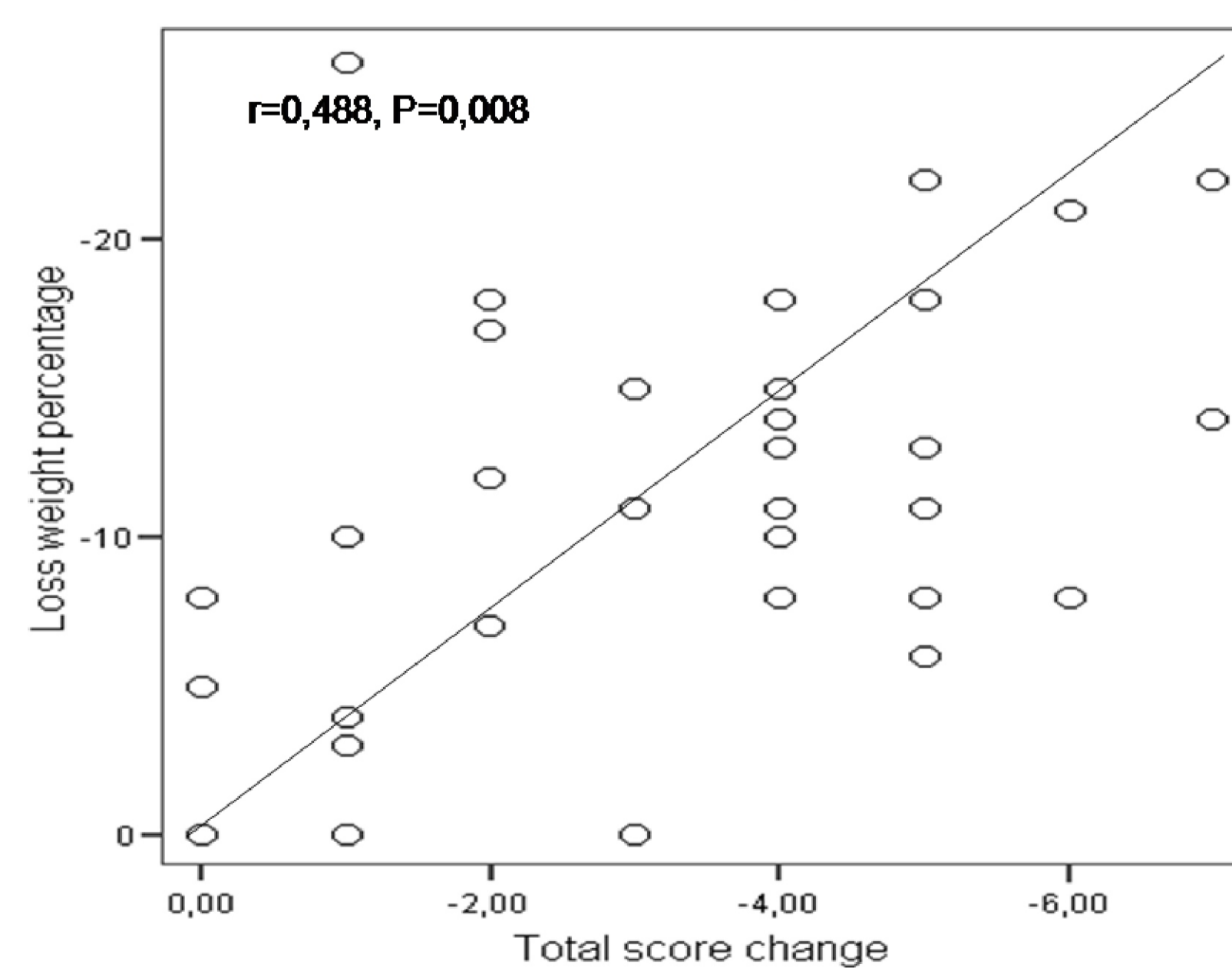


Figure 4. Correlation between loss waist and change in histological score

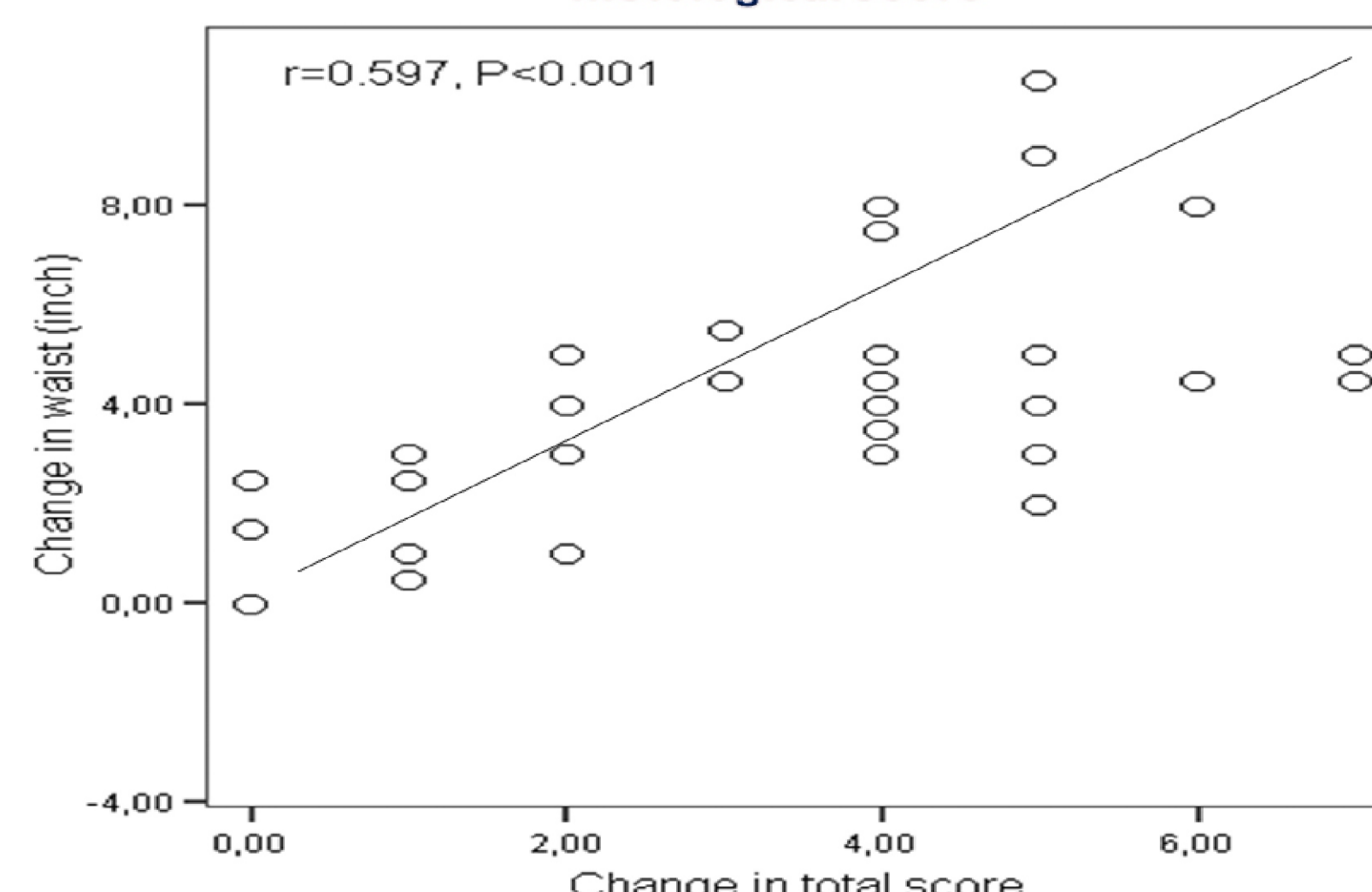
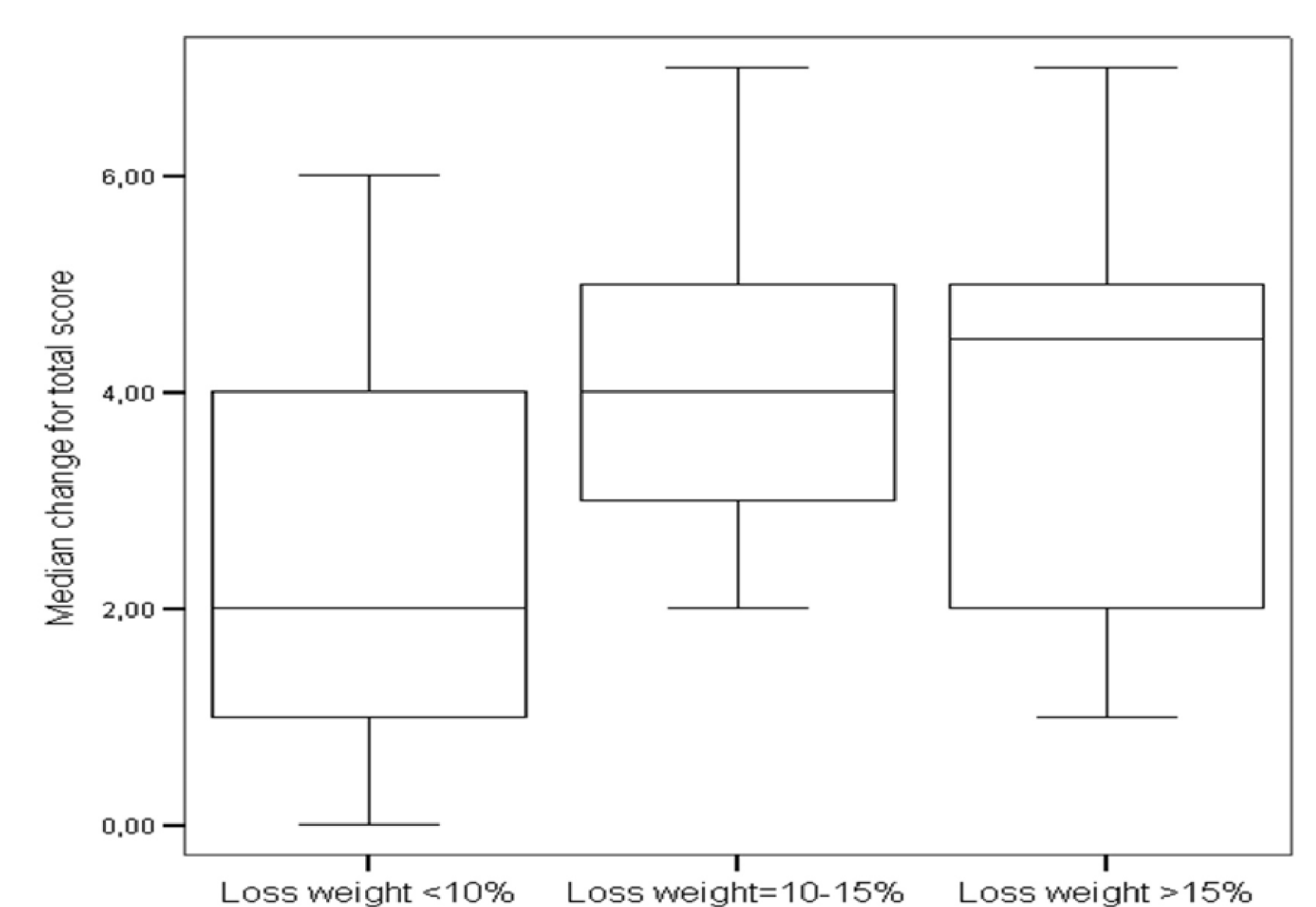


Figure 5. Association between the percentage of loss weight and change in histological score



Conclusions

- ▶ Our results indicate that treatment with hypocaloric diet and exercise can lead to notable improvement on anthropometric, biochemical and metabolic features of NASH, however, the triglycerides and uric acid concentrations were only improved by Viusid, diet and exercise combination
- ▶ The hypocaloric diet and exercise significantly improve the histological features of NASH, however, the administration of Viusid intensifies the improvements of histological findings, specially, on steatosis and inflammation.
- ▶ Viusid in combination with diet and exercise is an efficient and safety initial strategy of treatment in patients with non-alcoholic steatohepatitis

eridemia (129 ± 0.7 mg/dL versus 65 ± 0.4 , $p < 0.05$). Flow cytometry analysis revealed that circulating EPC decreased in HFD group (0.23% versus 0.46% in N group). Histopathology of liver showed HFD-induced granulocyte infiltration around the portal triad. GSH/GSSG ratio in liver also decreased significantly in HFD group (1.48 ± 0.03 versus N group = 1.81 ± 0.2 , $p < 0.05$). There were different 24 proteins down-regulated significantly in HFD group identified by proteomic analysis, included oxidative stress-related proteins such as peroxiredoxin-6, glutathione S-transferase, and regucalcin. The expression of proteins related to glucose metabolism, such as glucose-regulated protein and fructose-1,6-bisphosphatase, were also decreased in obese hamsters.

Conclusions: Obesity induced oxidative stress in the liver may down-regulate circulating EPC, and it may influenced the metabolism of glucose and lipid.

977 A ROLE OF THE DIET-INDUCED OXIDATIVE STRESS IN THE ONSET OF NASH

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Objective: Recently, nonalcoholic steatohepatitis (NASH) is attracting attention not only as a part of organ damage in metabolic syndrome but also as a factor to worsen insulin resistance. It is suggested that NASH results in the cirrhosis and progresses to liver cancer. We examined dietary effect and oxidative stress in pathogenesis of NASH. We used LOX-1tg/apoEKO mice in which higher oxidative stress and dyslipidemia are found by loading them with both high salt and fat diet (western diet).

Methods: We generated lectin-like oxidized LDL receptor-1 transgenic (LOX-1Tg) mice on apolipoprotein E-null mice (apoEKO). We loaded them with western diet to suppress renin angiotensin system (RAS) and examined oxidative stress, lipid metabolism and liver damage. Also we investigated the effect of blocking RAS.

Results: We confirmed NASH in LOX-1Tg/apoEKO mice group. Triglycerides in the liver and AST were elevated significantly and lipid metabolism exacerbated. Furthermore, the serum hyaluronic acid value (LOX-1WT/apoEKO; Normal diet (ND) 439 ± 58 [ng/ml], Western diet (WD) 659 ± 89 , LOX-1Tg/apoEKO; ND 345 ± 60 , WD 690 ± 71) and the expression of TGF- β 1 were elevated in LOX-1Tg/apoEKO mice loading them with western diet. By Masson's trichrome staining, we found type4 in Matteoni's classification and grade2, stage3 NASH in Brunt's classification. It was LOX-1Tg/apoEKO mice in comparison with LOX-1WT/apoEKO mice that recognized increases of oxidative stress in the liver significantly (LOX-1WT/apoEKO; ND 2299 ± 854 , WD 5648 ± 863 [RLU/mg], LOX-1Tg/apoEKO; ND 1301 ± 235 , WD 21188 ± 2911 : evaluated by lucigenin assay). And we confirmed elevation of local oxidative stress by 4-hydroxynonenal immuno-staining. Telmisartan, an angiotensin II receptor blocker (ARB), successfully improved all of parameters in the liver.

Conclusions: There are few reports of the typical NASH model mice. This model induced NASH in such a short term (eight weeks) loading them with western diet. High salt and fat loading increased oxidative stress and worsened liver damage. Interestingly, under high salt diet, RAS must be suppressed, however, ARB successfully reduced oxidative stress and concomitantly it reversed liver damage. It might be because the local angiotensin II is increased in the liver and/or partial PPAR γ agonistic action of telmisartan played a role.

978 EVALUATION OF TENOXICAM-INDUCED LIVER DAMAGE VIA USING IMMUNOHISTOCHEMICAL AND BIOCHEMICAL ANALYSIS

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Objective: Tenoxicam is a nonsteroid antiinflammatory drug (NSAID), which is completely eliminated in the liver. It has been reported that NSAIDs could lead to hepatotoxicity. In this study, we aimed to investigate the effects of tenoxicam on liver via using histological, immunohistochemical and biochemical methods.

Methods: 40 male Wistar albino rats were included in this study. Animals were separated into four groups as follows: Controls (Group I), tenoxicam (10 mg/kg/day) (Group II), tenoxicam (20 mg/kg/day) (Group III), tenoxicam (40 mg/kg/day) (Group IV). Tenoxicam was administered for 10 days. At the end of the study, rats were sacrificed under ketamine-xylazine anesthesia and liver tissues and blood samples were collected.

Results: In Group II, there was tenoxicam-induced liver damage, when compared with the control group. We have observed that this effect was more prominent in Group III, whereas the most significant hepatotoxicity effect was seen in Group IV. In immunohistochemical analysis, there was a dose dependent staining degree, which may suggest iNOS receptor intensity increases at higher dose levels. In biochemical analysis, there was a statistically significant increase in SOD and MDA levels, which are important markers of lipid peroxidation, in 10 and 20 mg/kg tenoxicam given groups than the controls.

Conclusion: These data indicate that NO can play an important role in tenoxicam-induced liver damage. Consequently, we can say that tenoxicam causes dose dependent damage in liver tissue with lipid peroxidation.

979 VIUSID, A NUTRITIONAL SUPPLEMENT, IN COMBINATION WITH DIET AND EXERCISE AS INITIAL STRATEGY OF TREATMENT IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS

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Introduction: No pharmacology therapy has conclusively proved to be effective for the treatment of non-alcoholic steatohepatitis (NASH). Dietetic and pharmacologic strategies to ameliorate the insulin resistance and improve the steatosis, inflammation and fibrosis have not demonstrated scientific evidence to approval its use in the clinical practice.

Aim: To evaluate the efficacy and safety of Viusid in association with diet and exercise in patients with NASH.

Methods: We randomly assigned 60 patients with liver biopsy-proven non-alcoholic steatohepatitis to 6 month of treatment with a hypocaloric diet (a reduction of 620 kcal per day to the calculated daily intake required to maintain body weight) plus aerobic exercise during 40 minutes daily and Viusid 3 sachets daily or hypocaloric diet, exercise and placebo. Hepatic histology was evaluated as primary end point. Kleiner, et al. score was used to analyze the histologic characteristics. It was performed before and after treatment. Biochemical, metabolic and anthropometric test were secondary end points.

Results: Forty two patients (70%) had paired liver biopsies. All biopsies were scored, blinded to the patient's identity and clinical condition, for individual histological features. There were major improvements in steatosis, necroinflammatory changes and fibrosis at the second biopsy ($P < 0.01$ for each group). Diet, exercise and Viusid, as compared with

diet, exercise and placebo, significantly reduced the total score mean (7.1 to 0.55 points for Viusid versus 8.1 to 3.9 points for placebo, respectively [$P=0.002$]). Administration of Viusid was associated with improvement in histologic findings with regards to steatosis ($P=0.018$), portal ($P=0.007$) and lobular inflammation ($P=0.025$), as compared with placebo, however, the reduction of the perisinusoidal and portal fibrosis did not significantly differ from that in the placebo group ($P=0.34$ and $P=0.32$, respectively). Triglycerides and uric acid concentrations were reduced in those patients assigned to Viusid in comparison to placebo ($P=0.01$ and $P=0.04$, respectively). Nauseas and diarrhea was reported in one subject who received Viusid.

Conclusions: Our results indicate that treatment with diet and exercise can lead to notable improvement on histological features of NASH, however, the administration of Viusid intensifies the improvements of histological findings, specially, on steatosis and inflammation.

980 MECHANISMS OF ISONIAZID-INDUCED HEPATOTOXICITY IN RATS

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Background: CYP consist of a superfamily that play an important role in the metabolism of a wide variety of xenobiotics, including drugs, carcinogens and environmental agents. The individual isoforms have different regulatory and functional characteristics including selective substrate specificity. CYP2E1 is of particular interest because it is involved in the metabolism activation of many drugs associated with toxic effects. Isoniazid is associated with hepatotoxicity by production its reactive intermediate metabolite via monooxygenase system with the cytochrome P450 2E1. Disulfiram inhibits enzyme induction and may thus interfere with the metabolism of drugs taken concomitantly. The purpose of this study was investigation the role of CYP2E1 in isoniazid-induced hepatotoxicity and the influence of disulfiram.

Methods: The effect of administration isoniazid or disulfiram on p-nitrophenol hydroxylase (p-NPH) activity (a marker of cytochrome P450 2E1) and content of cytochrome P450 in liver microsomes was studied using male rats. The liver tissue was collected, washed with cold saline, blotted dry and was homogenized. The homogenates were centrifuged, the pellets were resuspended and stored at -80°C until use.

Results: In pretreated isoniazid rats (dose – 100 mg/kg), the activities of p-NPH in liver microsomes was 4.66 ± 0.78 nmol/mg of protein compared with 1.58 ± 0.13 nmol/mg in control animals ($P < 0.005$). After parallel administration of disulfiram (dose 30 mg/kg) the p-NPH activity was 1.56 ± 0.24 nmol/mg of protein. Combined administration of both disulfiram and isoniazid decreased the activities of p-NPH to 2.19 ± 0.33 nmol/mg of protein. But had no effects on total content of cytochrome P450 in liver microsome fraction in comparison with control group. Conclusion It was shown thus inhibition of cytochrome P450 2E1 expression depressed isoniazid hepatotoxic action due to correction its toxic biotransformation with liver monooxygenase system.

981 WHEN CORTICOSTEROIDS FAIL: RESCUE TREATMENT WITH PENTOXIFYLLINE FOR ALCOHOLIC HEPATITIS

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Introduction: Corticosteroid (CS) treatment for alcoholic hepatitis (AH) remains controversial. Recent data has indicated that CS treatment can improve survival amongst patients with a Glasgow Alcoholic Hepatitis Score (GAHS) greater than or equal to 9. However some patients do

not appear to respond to CS, and these patients have a particularly poor outcome. Pentoxifylline (PTX) has also been suggested as a treatment of AH.

Aim: The aim of this study was to assess the effect of 'rescue' PTX therapy in patients in whom CS was ineffective or were discontinued.

Methods: We retrospectively identified those patients with AH treated with CS who did not respond to such treatment, or in whom CS treatment (prednisolone 40 mg) was discontinued on account of contra-indications. Non-response was defined as a failure of serum bilirubin to fall by 25% from baseline after 7 days of CS treatment. Survival to 84 days was recorded relative to the use of rescue treatment with PTX (400 mg tds for 4 weeks).

Results: 38 patients were identified: 34 were CS non-responders, 4 had CS therapy discontinued after developing sepsis. All patients had a GAHS greater than or equal to 9 and a DF greater than or equal to 32 at the start of treatment. 21 patients received PTX as treatment; 3 in addition to continued CS treatment, the remainder as alternative treatment. 6 of the non-PTX treated patients discontinued CS treatment, the remainder continued for 4 weeks. The 28 day survival for PTX and non-PTX patients was 52% and 76% respectively ($p=0.24$). The 84 day survival for PTX and non-PTX patients was 38% and 44% respectively ($p=0.97$). There was no survival difference on Kaplan-Meier analysis (HR 0.655; 95% CI 0.28, 1.52; $p=0.32$). Multiple logistic regression analysis failed to identify PTX therapy, the discontinuation of CS treatment, or the 7 day change in bilirubin as independent predictors of outcome.

Conclusions: Rescue treatment with PTX had no survival advantage for patients with AH who did not respond to CS, or in whom such treatment had to be discontinued. The management of these patients remains difficult and new therapeutic approaches need to be explored.

982 PHLEBOTOMY IS ASSOCIATED WITH AN IMPROVEMENT IN LIVER ENZYMES IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE AND INCREASED HEPATIC IRON STORES

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Introduction: Increases in hepatic iron stores have been implicated in the development of fibrosis in non-alcoholic fatty liver disease (NAFLD) (Gastroenterology 1998;114, 311–314). The effect of de-ironing on disease progression is unknown. The aim of this study was to assess the effect of venesection in NAFLD with mild iron overload on serum liver enzymes.

Methods: A review of patients attending liver clinic identified 16 patients with NAFLD who had been venesected for mild iron overload (defined on liver biopsy as \geq grade 1 iron on histology and/or hepatic iron concentration $\geq 20\mu\text{mol/gm}$ dry weight). Exclusion criteria were homozygosity for the C282Y mutations of HFE, alcohol intake in preceding year >20 g/d (women) or 40 g/d (men), and the presence of other liver diseases. All patients had received advice on life style modification. Data from case files were used to analyse the effect of venesection on serum alanine transaminase (ALT), ferritin, and haemoglobin.

Results: Subjects mean age was 50 years, 14 were men and 8 were C282Y heterozygotes. A mean of 11 (1 to 36) 500 ml venesections (Vx) were performed per subject, over a mean of 11 (3 to 32) months. Nine patients lost weight during Vx (mean 6 kg, range 1 to 22). Vx was not only associated with a significant fall in serum ferritin, but was also associated with a fall in ALT (see table). Mean haemoglobin following last Vx was 147 g/L (123 to 172).

Conclusion: In selected patients with NAFLD, venesection is associated with improvement in ALT, independent of concurrent weight loss. These data support randomised trials of Vx in NAFLD with mild iron overload.