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Six Months of Thiazolidine Carboxylic Acid Treatment Causes Significant Improvement in FibroTest in Patients with Non-Alcoholic Fatty Liver Disease

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Abstract

Background: Thioproline is a cyclic derivative of sulfuric amino acid with antioxidative and detoxifying functions. It is used in liver damage of varied causes, such as infectious, alcoholic, and metabolic.

Objectives: The presented study aimed to evaluate whether the six-month treatment with thioproline has an impact on liver fibrosis assessed with FibroTest and if there is an improvement in biochemistry results evaluating the liver condition.

Methods: Forty-four patients aged 18 to 70 years, with clinical symptoms of NAFLD without other diagnoses regarding liver were included in this prospective study. The patients received six months therapy with 600 mg thioproline daily. The serum for biochemical analysis was collected at the baseline and the end of the study. The Wilcoxon test was calculated to assess the significance of differences in that group of patients.

Results: The results of FibroTest decreased from 0.245 to 0.190 ($p<0.001$) after the treatment. Also, the decrease of GGTP and ALT activity, and alpha-2-macroglobulin concentration ($p=0.002$, $p=0.039$, and $p<0.001$, respectively) was observed. An increase in apolipoprotein A1 was found ($p=0.002$). The improvement in discussed results was not related to BMI loss, as the BMI change during the study period was not significant ($p=0.052$).

Conclusion: Administration of thioproline dosed 600 mg daily for six months was safe and resulted in a significant decrease in FibroTest, ALT, GGTP activity, alpha-2-macroglobulin concentration, and an increase in apolipoprotein A1 which suggests the regression of the inflammation in the liver.

Keywords: Thioproline; Liver fibrosis; FibroTest

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Abbreviations

A2M: Alpha 2-Macroglobulin; ALT: Alanine Aminotransferase; ApoA: Apolipoprotein A1; GGTP: γ-Glutamyl-1-Transpeptidase; GSH: Glutathione Reserves; Hap: Haptoglobin; LFT: Liver Function Test; NAFLD: Non-Alcoholic Fatty Liver Disease

Background

Based on the available literature and current research results, it is claimed that thioproline (thiazolidine-4-carboxylic acid, timonacic acid) in oral administration positively impacts the course of the disease in patients with acute and chronic liver diseases of various etiology and stages. The spectrum of use is very wide and includes liver damage due to infectious, alcoholic, and metabolic diseases [1]. Moreover, in one experiment using human hepatocytes cultured *in vitro*, a lower cytotoxic effect of paracetamol on liver cells was observed in the presence of thioproline when compared to the control group [2]. Thioproline is a cyclic derivative of the sulfuric amino acid with antioxidant and detoxifying properties, which translates into its hepatoprotective and anticancer effects [1,3,4]. In mitochondria, thioproline is converted to N-formyl cysteine which contains sulfhydryl; free Sulfhydryl (SH) groups provide the hydrogen necessary for the reduction of endo- and exogenous toxic metabolites leading to their inactivation. The antioxidative effect of thioproline

is secondary to the cysteine release and supports the renewal of the Glutathione Reserves (GSH) [3,5]. One of the key conditions that allow to successfully preventing oxidative stress at the cellular level is the presence of sufficient amounts of GSH. GSH is one of the most important and ubiquitous intracellular peptides that perform many functions, including detoxification of xenobiotics and/or their metabolites. Moreover, it influences the maintenance of the necessary saturation of proteins with thiol groups, as well as antioxidative protection by removing free hydroxyl radicals, providing a reservoir for cysteine, and modulating critical cellular biochemical pathways such as DNA synthesis [6,7]. One of the two main determinants of GSH synthesis is the availability of cysteine that may come from exogenous sources such as thioproline [7].

Non-Alcoholic Fatty Liver Disease (NAFLD) is one of the most common causes of permanent damage of this organ [8]. It is assessed that the frequency of NAFLD occurrence increases with age, and may affect even 40% of the population aged over 60 [9]. NAFLD characterizes by chronic and progressive character, which leads to liver fibrosis and cirrhosis in 10% to 20% of afflicted people [8,10]. The golden standard in assessing the liver fibrosis progression is still the biopsy with the pathologic evaluation, however, due to the invasive character and the risk of serious complications of the procedure, non-invasive methods based on analysis of particular biochemical and demographic variables tend to gain more and more importance. FibroTest is one of such tools [11].

Objectives

The aim of the study was to determine whether a six-month thioproline treatment with the daily dosage of 600 mg administered to patients with NAFLD would affect the liver fibrosis grade measured with FibroTest and whether it would have any effect on improving the results the of biochemical Liver Function Tests (LFTs).

Material and Methods

The prospective study was conducted on 44 men and women aged 18 to 70, who showed clinical symptoms of NAFLD, and whose alcohol consumption was proven not to exceed 30 g (men) and 20 g (women). Additionally, exclusion criteria included the presence of other documented liver diseases, e.g., viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, bile duct diseases, hepatocellular disease, and cases of use of drugs or substances that may affect liver function and obtained results.

Each participant was given 600 mg of thioproline divided into three 200 mg doses administered orally. The duration of the treatment was settled for 6 months. At the beginning and the end of the period of treatment with thiazolidine carboxylic acid serum of each patient was collected to determine the following parameters: Alanine Aminotransferase (ALT), α2-Macroglobulin (A2M), Haptoglobin (Hap), Apolipoprotein A1 (ApoA), γ-Glutamyl-1-Transpeptidase (GGTP) and bilirubin. In the further stage, the obtained results were used to mathematically calculate the algorithm for assessing the degree of liver fibrosis, the so-called Fibro-Test. The FibroTest value was calculated based on the formula below [12,13]:

$$4,467\log\left(A2M\left[\frac{g}{l}\right]\right)-1,357\log\left(Hap\left[\frac{g}{l}\right]\right)+1,017\log\left(GGT\frac{U}{l}\right)+0,0281\times age[years]$$
$$+1,737\log\left(Bil\left[\mu\frac{mol}{l}\right]\right)-1,184\times ApoA\left[\frac{g}{l}\right]$$
$$+0,301\times sex[women=0,men=1]-5,540$$

No medicine use-related adverse effects were observed in any of the participants, therefore there was no need for rechallenge or dose adjustment. All the patients completed the whole treatment and follow-up period.

Statistical Analysis

This section compares the numerical measures of hepatic steatosis and fibrosis in the studied patients before and after the treatment. Descriptive statistics allows presenting the distribution of the values of individual parameters before and after treatment, as well as changes in their values observed during treatment (treatment effects). The significance of the latter was assessed using the Wilcoxon test; the choice of a non-parametric test was dictated by the significant right-sided asymmetry of the parameters of fatty liver and fibrosis under study, and by the impossibility of using parametric tests. For the same reasons, the interpretation focused on the median, as the value could be overestimated by the measurements that differed in plus from the others.

Apart from the numerical measures, the fibrosis and steatosis level classification results, based on the obtained numerical values of the FibroTest measures, were presented and compared. However, it should be remembered that the converting numerical values into an adjective scale lead to a partial loss of information, thus there is a possibility that the purport of the results obtained after such categorization would differ from the original numerical data.

The result of treatment effects analyses was illustrated with scatter graphs, which allow for comparison of the parameters before and after the treatment, and with Bland-Altman plots, which show the distribution of treatment effects in relation to the mean base values and mean final values.

Ethics

Appropriate informed consent was obtained from each participant included in the study. The study protocol was approved by the appropriate local ethics committee (No 98/B/2018) and conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008).

Results

The analysis covered the results obtained from tests conducted on a group of 44 patients. The general characteristics of the studied population, both in terms of demographic and somatic aspects, as well as clinical parameters, are presented below (Table 1).

The majority of the patients qualified to participate in the study were characterized by inappropriate body weight, mostly with obesity (Table 2, 3). Regarding the obvious impact of biological sex on the somatic measurements, their distribution was presented in form of a comparison of descriptive statistics taking cognizance of the division into men's and women's groups. The presentation concerns parameters taken at the beginning of the therapy because during the treatment process (six-month period) no significant changes in body weight, BMI, or other somatic measurements occurred.

Table 1: Examined patients: Basic data.

	Mean or percentage
Men	24 (54.5%)[1]
Age [years]	47.0 (9.2)[2]
Diabetes	18 (40.9%)[1]

[1]Population size (percentage); [2]Standard Deviation

Table 2: Somatic measurements of the examined group of patients.

Somatic features (before treatment)	Sex									
	male					female				
	$\bar{x}$	Me	*s*	min	max	$\bar{x}$	Me	*s*	min	max
Height [cm]	162.8	160	5.9	154	176	177.4	177	4.7	170	188
Body weight [kg]	87.3	84.6	16.4	58	120	90.9	88.9	12.8	70	120
BMI [kg/m^2]	32.7	32.9	4.1	24.5	40.8	28.9	29.1	3.7	22.1	37
Waist [cm]	102	101	11.5	83	124	103.6	102.5	10.3	87	121
Hips [cm]	113.1	112.5	13.1	89	140	104.3	105	7.1	89	120

Me: Median; *s*: Standard Deviation

Table 3: Division of patients into groups with normal body weight, overweight and obesity, with regard to gender.

Classification due to BMI (before treatment)	Sex (*p*=0.1495)		Total
	man	woman	
Normal body weight	1 (5.0%)	4 (16.7%)	5 (11.4%)
Overweight	5 (25.0%)	10 (41.7%)	15 (34.1%)
Obesity	14 (70.0%)	10 (41.7%)	24 (54.5%)
Total	20	24	44

Table 4: FibroTest score before treatment and after the six-month follow-up period.

FibroTest	$\bar{x}$ (95% p.u.)	Me	*s*	min	max
Before treatment	0.245 (0.187; 0.303)	0.190	0.190	0.030	0.890
After treatment	0.190 (0.138; 0.242)	0.135	0.172	0.020	0.830
Treatment effect (*p*=0.0000***)	-0.055 (-0.073; -0.037)	-0.045	0.059	-0.190	0.060

Me: Median; *s*: Standard Deviation

Table 5: Comparison of FibroTest scores before and after the six-month treatment.

After treatment *vs.* before treatment	Number	Percentage
Decrease	35	79.5%
No changes	3	6.8%
Increase	6	13.6%

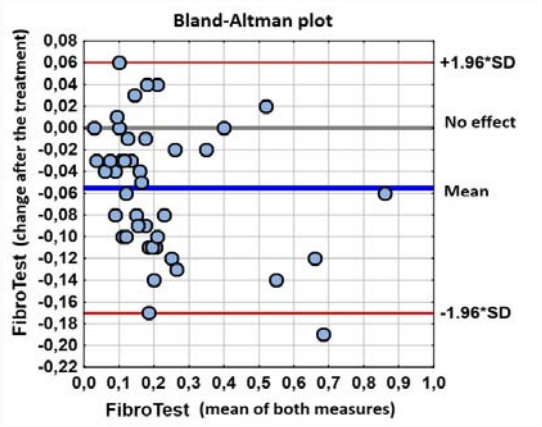

Figure 1: Changes in FibroTest values before treatment and after the six-month period of treatment.

The median BMI among women equals 32.9, which means that over a half of them is obese (according to WHO classification BMI ≥ 30), and among men, the median BMI places a bit below 30, which meant that slightly less than half of them is obese. In the women's group as many as 70% are obese, and among men 40%. Almost all the patients are overweight; only every twentieth woman and every sixth man's BMI fell within the "normal weight" range.

After the six-month treatment with the tested drug, the decrease in FibroTest score was statistically significant (p=0.0000***). The average drop equaled 0.055, while the maximal came to 0.190. Maximal drops reached even 80% of the source score; however, there were some cases of increase in FibroTest parameter score (Table 4, 5 and Figure 1, 2). The comparison of the F fibrosis stage classification based on the FibroTest parameters shows a positive shift towards the baseline stage of fibrosis progression (F0) that occurred during the treatment with the medication. Analysis with a McNemar test confirms that the changes in fibrosis-related parameters are statistically significant (p=0.0159*) (Figure 3).

An analysis of the influence on the obtained results of selected biochemical parameters used to calculate the values of the FibroTest parameters, body weight, and BMI was conducted. The changes in the level of selected laboratory parameters during the treatment with the tested drug, including the parameters that are used to calculate the FibroTest were analyzed; in particular: GGTP, bilirubin, alpha-2 macroglobulin, apolipoprotein A1, haptoglobin, ALT, body weight, BMI.

The changes in values of the FibroTest results after the treatment period were statistically significant, however, it is interesting which particular parameters used in the calculation formulas of these measures also changed.

Table 6 provides information on the mean level of each parameter before and after six months of treatment, as well as their average change due to treatment. Mean values were given with a 95% confidence interval. Due to the presence of a fairly large asymmetry in the distribution of some parameters that may affect the reliability of their mean-based assessment, the values of the median and standard

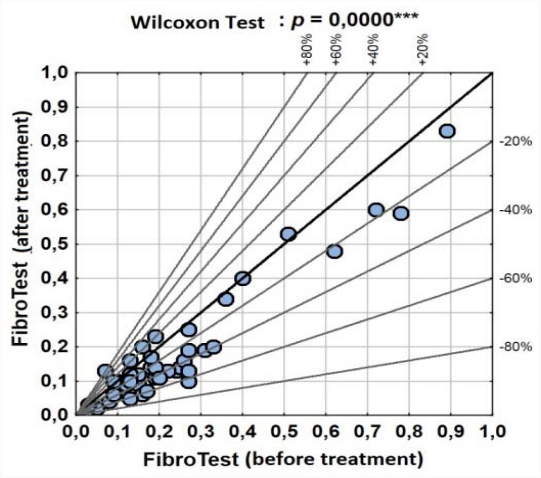

Figure 2: Changes in FibroTest values before the treatment and after the six-month treatment period.

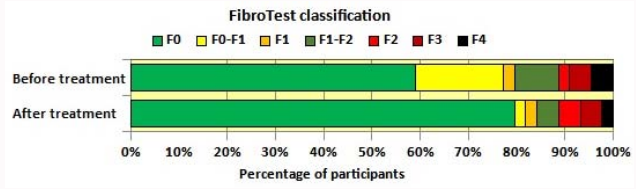

Figure 3: Changes in METAVIR fibrosis score before and after the treatment.

deviation for each of the measurements were also provided. The significance of treatment effects was assessed using the Wilcoxon test.

The GGTP values decreased significantly after the treatment: The median difference equaled- 3 IU/l. The mean change, which may be somewhat distorted by the presence of a few outliers, equaled- 14.1 IU/L. Bilirubin levels also decreased slightly after treatment, but this effect was not statistically significant (p>0.05). The treatment-related decrease in the concentration of α2-macroglobulin was significant (on average by 0.14 g/l). The treatment effect was highly significant (p-value <0.0001). Similar conclusions apply to apolipoprotein concentrations that increased after treatment (p=0.0024; mean change 0.07 g/l). No change in the haptoglobin concentration was observed during the treatment. ALT activity decreased significantly after treatment: mean change equaled- 11.9 IU/L and median change was- 4.5 IU/L. After the treatment, a statistically significant decrease in body weight was also observed. Also, the BMI value slightly decreased after the treatment; the treatment effect on the value of this index is only close to the level of statistical significance (p=0.0524).

Discussion

Thioproline is a substance that has been known for many years; in the early 1980s it was thoroughly studied for its antioxidative potential for use in cancer therapy [14,15], as an influenza virus neuraminidase inhibitor [16], thioproline derivatives were used as tyrosinase inhibitors [17] or as agents which increase the activity of catalase [18]. Then, taking into account the influence of thioproline on the activity of the antioxidant enzymes [1,18-20], its influence as a precursor or regulator of glutathione synthesis was examined: its effectiveness in this aspect was assessed through tests on animals' studies in alcohol-induced liver damage [21], as well as through tests on humans in studies of toxic, paracetamol-induced liver damage. Regardless of the liver dysfunction, research studies conducted in the 1990s aimed to assess the effectiveness of this substance as a potential drug against influenza virus neuraminidase. While the substance is not new and there are studies regarding its use in the treatment of liver disease, the authors did not find any studies on the effects of this substance in the treatment of non-alcoholic fatty liver disease, which makes this, study a precursor to assessing the effects of thiazolidine-4-carboxylic acid use in the NAFLD.

According to the guidelines issued in 2019 by the Polish Group of Experts on NAFLD [22], the basic recommendation in NAFLD treatment is the lifestyle change which includes the bodyweight reduction (in the case of overweight or obesity), restriction in the consumption of simple carbohydrates and simple lipids, and the recommendation of drinking 2 cups of coffee per day. In the case of NAFLD without NASH and fibrosis, it is recommended to limit the therapeutic management to concomitant diseases, while if patients are diagnosed with NASH, it is suggested to include vitamin E supplementation (unless the patient suffers from type 2 diabetes) or pioglitazone (in patients with type 2 diabetes mellitus). There are also suggestions that patients with advanced NAFLD (NASH with fibrosis) should not be treated with hepatoprotective drugs, thioproline included [22]. Such suggestions are explained by the lack of a significant effect on hepatic fibrosis, and, provided that a significant decrease in ALT activity is observed, hepatoprotective treatment should be considered while pending the introduction of drugs that inhibit the progress of NAFLD [22]. The presented results of the study suggest that thioproline is effective in reducing

Table 6: Clinical and biochemical parameters before and after the six-month treatment.

Parameter	Before treatment			After treatment			Treatment effect			
	Mean (95% p.u.)	Median	Std. dev.	Mean (95% p.u.)	Median	Std. dev.	Mean (95% p.u.)	Median	Std. dev.	*p*
Body weight [kg]	893 (84.9; 93.7)	86.1	14.5	88.7 (84.0; 93.4)	85.6	15.4	-0.6 (-2.1; 1.0)	-0.5	5.1	0.0452*
BMI	30.6 (29.3; 31.9)	30.4	4.3	30.4 (28.9; 31.9)	30.5	4.9	-0.2 (-0.7; 0.4)	-0.2	1.8	0.0524
GGTP [IU/l]	89.7 (55.0; 124.5)	46.5	114.4	75.6 (44.9; 106.3)	40.5	101.0	-14.1 (-39.3; 11.0)	-3	82.8	0.0017**
Bilirubin [µmol/l]	14.0 (12.0; 15.9)	12	6.4	13.0 (11.1; 14.8)	12	6.2	-1.0 (-2.2; 0.2)	0	4	0.1023
Alpha-2-macroglobulin [g/l]	1.60 (1.46; 1.73)	1.57	0.45	1.45 (1.32; 1.59)	1.35	0.44	-0.14 (-0.19; -0.09)	-0.12	0.17	0.0000***
Apolipoprotein Al [g/l]	1.45 (1.39; 1.51)	1.47	0.2	1.52 (1.45; 1.60)	1.53	0.25	0.07 (0.03; 0.12)	0.08	0.15	0.0024**
Haptoglobin [g/l]	1.23 (1.08; 1.38)	1.19	0.49	1.25 (1.10; 1.41)	1.26	0.51	0.02 (-0.07; 0.11)	-0.01	0.29	0.7705
ALT [IU/l]	51.7 (37.8; 65.6)	43.5	45.6	39.8 (33.5; 46.2)	33.5	20.9	-11.9 (-22.8; -0.9)	-4.5	36	0.0385*

BMI: Body Mass Index; GGTP: Gamma-Glutamyl Transpeptidase; ALT: Alanin Aminotransferase
*p<0.05; **p<0.01; ***p<0.001

the FibroTest values, which is most likely due to its beneficial effect on the regression of fibrotic and inflammatory changes in the liver tissue. Additionally, the use of timonacic acid does not contradict the current recommendations of the Polish NAFLD Experts Group, because during the six month follow up, a significant decrease in ALT activity in the study group was demonstrated, i.e., from an average activity of 51.7 U/l to an average of 39.8 U/l (p=0.0385). The decrease in ALT activity with a BMI index that was not changed significantly is also valuable information: It indicates the effect of thymonactic acid, not the modification of the lifestyle and weight reduction.

The conducted study, results of which were limited due to a small sample of respondents, should, however, be considered preliminary, yet valuable because it indicates the direction in which further research could be conducted. In search for drugs that inhibit the progress of NAFLD, any substance which is proven to reduce ALT activity, but which seems to be more important, to cause regression of fibrosis, seems to be extremely important. Therefore, the continuation of the research on thioproline in NAFLD treatment seems even more justified. For this purpose, however, the follow-up period should be significantly extended, because it is known that while a decrease in ALT activity or a decrease in the value of inflammatory parameters may occur in a short time, the regression of hepatic fibrosis is a long-term process.

Conclusions

1. Six-month therapy of thioproline in the daily dosage of 600 mg, used in people suffering from NAFLD, significantly decreases the stage of liver fibrosis assessed with FibroTest.

2. Six-month thioproline therapy period reduces the ALT and GGTP activity and the α2-macroglobulin concentration, as well as increases the concentration of A1 apolipoprotein. This suggests regression of the inflammatory fibrosis which leads to liver cell damage.

3. Inhibiting the progress of fibrotic changes in the liver tissue of people suffering from NAFLD by administering the thioproline therapy requires confirmation in further research.

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