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The effects of N-acetylcysteine on hepatic, hematologic, and renal parameters in cirrhotic patients: a randomized controlled trial

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ABSTRACT

Aim: To evaluate the effects of N-acetylcysteine (NAC) supplementation in cirrhotic patients.
Background: Chronic hepatic inflammation leads to fibrosis and cirrhosis through various mechanisms such as oxidative stress. NAC is one of the intracellular precursors of glutathione that can degrade most reactive oxygen species. Recently, the beneficial effects of NAC in animal and human studies on preventing liver injury progression and improving liver function have been examined. However, more studies on human subjects are still required.
Methods: Well-known cirrhotic patients with a specific etiology and aged 18 to 70 years who referred to the gastrointestinal clinic of Ayatollah Taleghani Hospital from December 2018 to December 2019 were enrolled in the present randomized double-blind controlled trial. Patients in the intervention group received NAC tablets at a dose of 600 mg daily, and the control group received a placebo. Demographic data, medical characteristics, and Child-Pugh and MELD scores evaluated at baseline and after 6 months.
Results: Totally, 60 patients completed the present study (30 patients in the intervention group, and 30 patients in the control group). Hematological and biochemical parameters were normal in both groups with no significant differences at baseline and 6 months after intervention values. Moreover, the renal function indicators including serum creatinine (Cr) and urea (BUN) decreased significantly after intervention. Hepatic parameters also decreased significantly 6 months after intervention. Decreases in the renal and hepatic parameters 6 months after baseline in the control group were not statistically significant.
Conclusion: The results of this study showed that NAC improved hepatic and renal function by decreasing serum urea and creatinine levels but had no significant effect on hematological and biochemical parameters. Furthermore, NAC significantly improved hepatic profiles by decreasing ALT, AST, and ALP in the liver enzymes between the intervention and control groups. Moreover, NAC caused a significant decrease in Child-Pugh and MELD scores.

Keywords: N-acetylcysteine, NAC, Cirrhosis, Child-Pugh score, MELD score.

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Introduction

Chronic hepatic inflammation leads to fibrosis and eventually cirrhosis through various molecular

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mechanisms. Existing antiviral, anti-inflammatory, and immunosuppressive treatments can partially prevent progression or persistence, and it may even return to liver fibrosis depending on the context of the cirrhosis (1). Among the cellular processes that affect fibrosis of the liver cells are chronic inflammatory and oxidative stress. During these processes, reactive oxygen species and activated cascades of inflammatory cytokines cause cell damage in the liver. Thus, it seems antioxidant drugs can affect improvement in this area (2). N-acetylcysteine (NAC) is one of the intracellular precursors of glutathione that can degrade most reactive oxygen species by activating the glutathione transferase enzyme and improving blood supply and nitric oxide (NO) levels and metabolites. Increased tissue oxygen levels will accelerate healing of damaged tissue (3). Many potential clinical applications for NAC have been established in a variety of clinical settings, including definitive therapeutic applications for pulmonary fibrosis, cystic fibrosis, and acetaminophen poisoning (4). In recent years, the antioxidant effect of NAC has been extensively evaluated in studies, and because of its role in damping oxidative stress, its effect and mechanism on reducing liver damage have been studied in many animal and human studies. Nonetheless, literature about humans in RCT design is still fairly rare (5-8). According to these studies, NAC not only involve in reduced glutathione and nitric oxide (NO), but also serve as a methyl group donor so that it aims to methylation of nucleic acids, phospholipids, histones, biogenic amines, and proteins. Moreover, NAC is a well-known anti-fibrotic agent, as it blocks transforming growth factor-beta (TGF-β) signaling in fibrogenic cells, according to the literature (8). Overall, results confirm the efficacy of NAC in the process of liver injury through increasing glutathione levels and super oxidase factors, decreasing lipooxidation and nitrate, fibronectin, inflammatory factors, preventing glutathione transferase enzyme depletion, preserving hepatic glycogen stores, and inducing oxidant / antioxidant balance (5-9). Despite the multitude of animal studies on NAC in liver injury, human studies in this field are much more limited and have been performed on specific groups of patients with liver injury. Results of a published meta-analysis of NAC administration in acute liver injury confirmed the significant effect of this supplement on the survival rate of patients with primary liver injury and patient survival after liver transplantation (10). Given the positive effects of NAC in animal and human studies in preventing the progression of liver damage and improving liver function, and the absence of study similar to the current one, the effects of this supplement on hepatic, hematologic, and renal parameters in patients with cirrhosis at an early stage were investigated.

Methods

Patient selection; inclusion and exclusion criteria

The current study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, and the study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Well-known patients with cirrhosis, defined as late stage progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules (11), with the specific etiology of being aged 18 to 70 years who referred to the gastrointestinal clinic of Ayatollah Taleghani Hospital from December 2018 to December 2019 were enrolled in the present randomized double-blind controlled trial. Informed consent was obtained from all participants. Patients with active infection, gastrointestinal bleeding, known cancer and severe chronic comorbidity, and encephalopathy were excluded. The healthcare provider who prescribed the supplement and placebo as well as the patients were blinded to the randomization. At baseline, patients who met all of the inclusion criteria and none of the exclusion criteria were assigned using computer-generated randomization.

Intervention

Patients in the intervention group received NAC tablets at a dose of 600 mg daily. Participants in the control group received a placebo made by Oh Sina

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Company and similar to the supplement given to the intervention group once daily.

Outcome measurements

At baseline, whole blood tests, liver function tests (bilirubin, albumin, prothrombin time, transaminases), and kidney function tests (creatinine, urea and electrolytes) were conducted. At the end of the study (6 months after study initiation), these values were measured again and interpreted by the clinical diagnostic laboratory of Ayatollah Taleghani University Hospital. Moreover, Child-Pugh and MELD scores for all patients were calculated at baseline and 6 months after study initiation. Then, these values were compared between the intervention and control groups. The mentioned scoring systems are gold standards for the assessment of prognosis in liver cirrhosis (12). All patients were visited 3 and 6 months after study initiation to be evaluated for possible supplement side effects or clinical complications. They were also followed up monthly through telephone contact to monitor their adherence to supplementation.

Statistical analysis

In accordance with the existing guidelines (13), no violations of study protocol in population selection, patient entry, allocation, implementation of plan, and intervention occurred. Therefore, the present study was set based on per protocol analysis; however, the present study examined the actual received effect of considering intervention on patients during the study follow-up period and did not consider assigned effect

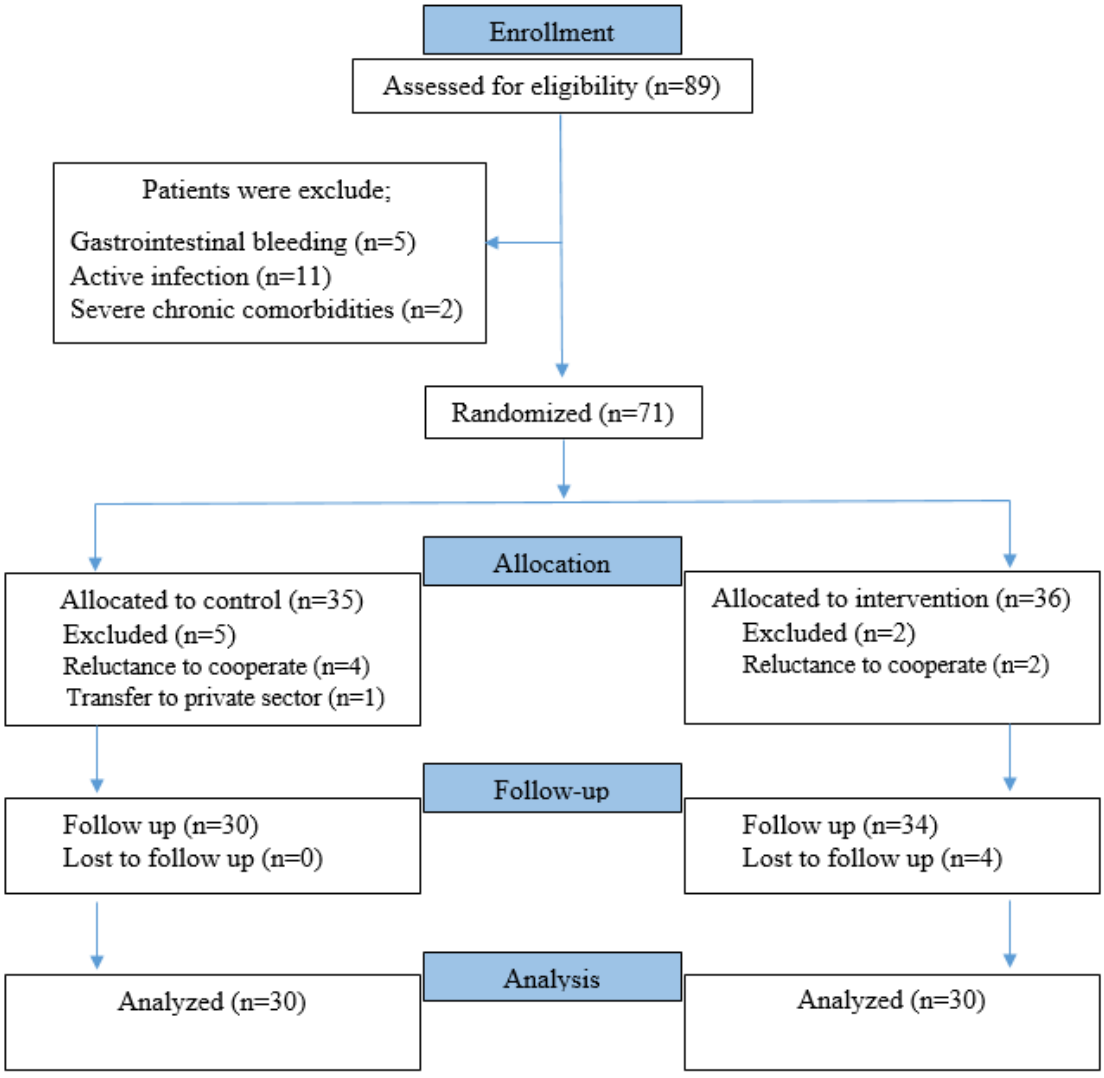

Figure 1. CONSORT flow diagram

on patients who had violated or withdrawn from the study for any reason. Given what was stated, this study did not have an intention-to-treat approach, which in turn could be considered as a study limitation. The data were analyzed using the statistical package IBM SPSS, version 22.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, New York, USA). The normality of distribution of the measured variables was checked using Kolmogorov–Smirnov and Shapiro–Wilk tests. Descriptive statistics for quantitative data with normal and non-normal distributions were presented using mean±SD and median (Q1-Q3) values, respectively. Qualitative data were reported as frequency and percentage. Independent and paired t-test or their nonparametric peers, i.e., Mann-Whitney and Wilcoxon tests were used to evaluate the change in response variables with normal or non-normal distribution, respectively. All tests were performed at the significance level of lower than 0.05.

Results

In total, 60 eligible patients completed the study (30 patients in the intervention group, and 30 patients in the control group). The patient flowchart shown in Figure 1 illustrates the allocation in each group based on CONSORT flow diagram (Figure 1). Table 1 presents the base characteristics of the patients. As Table 2 shows, hematologic and biochemical variables at baseline and 6 months after the study had no significant differences within or between the intervention and control groups. The results revealed that mean serum creatinine levels 6 months after the study compared with the baseline had a marginal reduction in the intervention group which was not statistically significant. This pattern, however, was inverse in the control group (Table 2). Moreover, mean BUN levels 6 months after study initiation were decreased in the intervention group, although this decrease was not statistically significant. Interestingly, mean BUN levels in the control group 6 months after study initiation were statistically significantly increased. Comparing the two groups 6 months after study initiation revealed that mean BUN levels were substantially lower in the intervention group than in the control group, although this difference was only marginally significant (Table 2); perhaps with a larger sample size a statistically significant effect would have been seen. Liver transaminases (alanine transaminase, ALT and aspartate transaminase, AST) decreased statistically significantly in patients in the intervention group. These enzymes were also decreased in the control group at the end of the study, however, the difference were not statistically significant (Table 2). Alkaline phosphatase (ALP) was significant decreased in both groups (Table 2). Child-Pugh scores from the intervention and control groups were compared before and after the intervention. In both groups before and after the intervention, the highest number of people were in group

Table 1. Demographic and baseline characteristics of study population (n=30)

Variables	Intervention group	Placebo group	*P*-value
Age, years, mean±SD	55.80±12.60	56.30±14.50	0.60*
Sex, male, n (%)	22 (73.3%)	13 (43.3%)	0.50**
BMI, Kg/m^2, mean±SD	26.32±5.20	26.47±6.43	0.20*
Smoker [a], n (%)	26.7%)(8	26.7%)(8	1.00**
Opioid addict [a], n (%)	16.7%)(5	6.7%)(2	0.42**
Alcoholic [a], n (%)	10%)(3	10%)(3	1.00**
Etiology, n (%)			0.83**
NASH	12 (40%)	11 (36.7%)	
Alcoholic	9 (30%)	8 (26.7%)	
Viral	6 (20%)	9 (30%)	
Autoimmune	3 (10%)	2 (6.7%)	0.35**
Medications, n (%)			0.30**
Spironolactone			0.77**
Furosemide	26 (89.7%)	29 (96.7%)	0.27**
Propranolol	13 (43.3%)	17 (56.7%)	0.16**
Lactulose	9 (30%)	8 (26.7%)	
Acetaminophen	12 (40%)	8 (26.7%)	
	7 (23.3%)	12 (40%)	

*Results from the independent t-test, **results from the Chi-Square Test

[a] Results were gathered as qualitative variables through patients interview and record history of use as a binary variable for each smoking, opioid addiction, and alcohol consumption variable; i.e. Yes/No. Abbreviations: BMI, body mass index; NASH, nonalcoholic steatohepatitis

A (Figure 2). The mean Child-Pugh scores in the intervention group were 7.4±1.2 and 5.8±0.8 before and after treatment, respectively. In the control group, the mean Child-Pugh scores were 5.6±1.8 and 5.1±2.2 before and after treatment, respectively. Comparisons based on the Chi square test showed that more patients had an A level Child-Pugh score after intervention compared with before intervention. Moreover, Child-Pugh B and C level scores were decreased statistically significantly 6 months after intervention compared with before intervention (p-value=0.01) (Figure 2). The MELD scores of the intervention and control groups were compared before and after the intervention. The median (Q1-Q3) MELD score in the control group before and 6 months after the intervention was 12.5 (8-17), and 10 (7-15), respectively (p-value=0.07). This value for the intervention group before and 6 months after NAC supplementation was 12 (9.25-16), and 9.5 (8-11), respectively (p-value=0.009). The median MELD score in both groups decreased six months after the initiation of the intervention, and this difference was statistically significant in the intervention group (p-value=0.009).

Discussion

The results of the present study revealed no significant differences within or between the intervention and control groups in hematologic and biochemical variables at baseline and 6 months after the study. Moreover, some hepatic and renal parameters were measured in the present study at baseline and 6 months after intervention. Mean serum creatinine levels and BUN 6 months after the study showed a decrease in the intervention group compared with baseline, but the difference was not statistically significant. Changes in these levels in the control group were incremental. Six months after the intervention, mean BUN levels in the intervention group were substantially lower than those in the control group, although this

Table 2. Hepatic, hematologic, and renal parameters in the studied cirrhotic patients before and 6 months after treatment

Parameters	Intervention group (n=30)		Placebo group (n=30)		*P*-value *	
	Before	After	Before	After	Before	After
WBC, 10^3 /uL	5.44± 1.70	5.89±3.30	7.13±6.7	5.93±2.1	0.13	0.61
P-value **	0.51		0.35			
Hgb, g/dL	12.63±2.30	12.49±2.30	12.28±2.6	12.8±1.8	0.63	0.31
P-value **	0.53		0.12			
Plt, 10^3 /uL	128.4±71.5	127.6±67.8	143.8±115.1	147.8±123.6	0.49	0.39
P-value **	0.96		0.54			
PT, Sec	13.77±2.9	12.97±3.1	13.23±3.9	12.51±2.1	0.34	0.41
P-value **	0.41		0.39			
INR	1.38±0.4	1.37±0.4	1.29±0.2	1.24±0.3	0.76	0.45
P-value **	0.64		0.30			
Sodium, mmol/L	138.9±3.1	134.3±5.2	138.6±3	139±4.3	0.56	0.32
P-value **	0.44		0.60			
Potassium, mEq/L	4.4±0.5	4.22±0.3	4.15±0.4	4.17±0.3	0.80	0.78
P-value **	0.97		0.96			
Albumin, g/dL	3.65±0.5	3.81±0.8	3.8±0.5	3.78±0.6	0.73	0.71
P-value **	0.86		0.71			
BUN, mg/dL	15.20±6.50	14.83±4.50	14.7±4.70	17.97±7.90	0.51	0.08
P-value **	0.94		0.002			
Creatinine, mg/dL	1.5±0.26	1.03±0.24	0.98±0.38	1.03±0.48	0.72	0.93
P-value **	0.78		0.27			
ALT, U/L	71.3±19.7	41.17±40.2	60.7±5.2	40.09±5.1	0.62	0.93
P-value **	0.04		0.11			
AST, U/L	109±15.7	43.76±26.4	64.8±9.1	45.9±3.9	0.28	0.94
P-value **	0.03		0.42			
ALP, U/L	336.8±23.2	248±11.8	309.7±14.3	257.3±90.2	0.56	0.81
P-value **	0.04		0.03			
Bilirubin T, mg/dL	3.2±2.6	1.87±1.8	1.99±1.8	1.6±1.4	0.49	0.59
P-value **	0.34		0.15			
Bilirubin D, mg/dL	1.8±1.24	0.56±0.50	0.98±0.8	0.5±0.3	0.44	0.67
P-value **	0.11		0.12			

*Results from the independent t-test, **Results from the paired t-test

Abbreviations: WBC, white blood cells; Hgb, hemoglobin; Plt, platelet; PT, prothrombin time; INR, international normalised ratio; BUN, blood urea nitrogen test; ALT, alanine transaminase; AST, aspartate transaminase

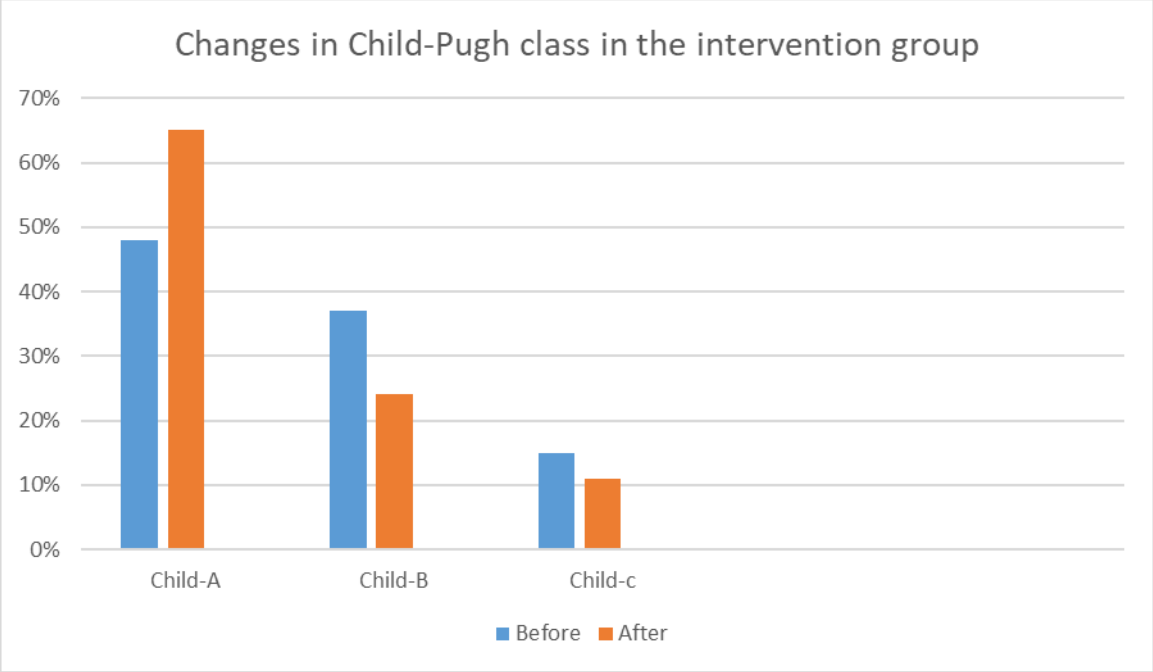

Figure 2. Changes in Child-Pugh class in the intervention group

difference was only marginally significant. Liver enzymes including ALT, AST, and ALP showed statistically significant decreases in the intervention group compared with the control group. Patient Child-Pugh and MELD scores were better in the intervention group compared with the control group at the end of the study.

Long-term liver damage results from various reasons, such as a high fat diet, sedentary lifestyle, alcohol addiction, viruses, and autoimmunity, which eventually lead to liver fibrosis, also known as liver cirrhosis or end-stage liver disease (14). Some coexisting morbidities could occur as either a direct or a secondary outcome of cirrhosis and may accelerate mortality. These morbidities could involve critical organs such as the kidney and lungs. Thus far, evidence illustrates that renal failure known as hepatorenal syndrome is a common complication in cirrhotic patients that probably originates from elevated circulating proinflammatory cytokine levels (15). Hepatopulmonary syndrome is another common consequence of end-stage liver disease with a prevalence of 4% to 32% in adult patients (16). Liver cirrhosis followed by portal hypertension causes a deficit in intestinal perfusion, which, in turn, leads to the overexpression of vasoactive agents such as nitric oxide (NO). Many studies have concluded that excess NO is a leading cause of hepatopulmonary syndrome (16-18). Evidence indicates that NAC, well-known as an antioxidant agent, could have an inhibitory effect on NO production; hence, it can be an effective supplement for use in patients with this condition (19). One study has shown that intravenous administration of NAC could reduce incidence of acute kidney injury, improve renal and liver function, and enhance outcomes in cirrhotic patients undergoing major abdominal surgeries (20). Today, there is a growing body of evidence that suggests the beneficial effects of NAC on neurodegenerative disorders, hepatic diseases, cardiovascular abnormalities, kidney injury, and even for use in cosmetics (21). A recent animal study demonstrated the renoprotective effects of NAC in cirrhotic animal models. Based on this study, the underlying renoprotective mechanisms seem to lie in the improvement of mitochondrial function and cellular redox state induced by NAC (21). Another study stated that NAC significantly improved tissue histopathological alterations and alleviated oxidative stress in cholestatic animals (22). A meta-analysis of 22 clinical trials and 1714 patients examined the impact of using hepatoprotective drugs with and without antiretroviral drugs on the maintenance of hepatic function and fibrosis in patients with hepatitis B (23). The results showed that the combination of antiretroviral and hepatoprotective drugs produced significantly better results than the

antiretroviral drugs alone in improving liver function and hepatic fibrosis. Moreover, normalization of ALT levels and bilirubin reduction in the two liver protective drugs were 25% better than using only one drug. In the mentioned study, NAC was better at lowering ALT than either ursodox or silibinin, while ursodox was more effective in reducing bilirubin than the other two drugs (23). The current results, consistent with those of the mentioned meta-analysis, indicate that NAC could have significant beneficial effects on liver function. In their randomized controlled trial reported in 2020, Kakaei et al. (24), evaluated the effects of NAC on liver and kidney function tests after surgical bypass in obstructive jaundice. Their results showed postoperative intravenous administration of NAC (200 mg/kg per hour in the first 8 h, followed by 100 mg/kg per hour for another 16 h and the same dose for another 24 h) was related to greater decreases in mean serum AST, ALT, ALP, gamma-glutamyl transferase, and bilirubin levels in the study group compared to the control (24). Similar to the mentioned study, the current results also support a more decreased paradigm in liver enzymes and markers, other than gamma-glutamyl transferase which was not measured in the current study, in the NAC group than in the control group. As Kakaei et al. (24) and other researchers (20, 25) have concluded, we also found that decreasing changes in the parameters of routine kidney functions, i.e., Cr and BUN, did not have statistically significant effects. However, our study showed that the decrease in BUN 6 months after daily administration of 600 mg NAC in the intervention group compared to the control neared statistical significance. Moreover, the mean±SD of BUN level had statistically significant increase in the control group, a result partially supported by some previous studies (26). A meta-analysis of clinical trials published in 2021 (27) about NAC for chronic kidney disease showed that the NAC group had statistically significantly better kidney parameters than the control group. As regards kidney parameters, the current results are more comparable with the meta-analysis relative to other mentioned articles (20, 25). In this meta-analysis (27), similar to the current study, the intervention period often was long (weeks to months), but other mentioned studies often had short study periods (a few days after administration). In the current study, the mean±SD of BUN level in the NAC group 6 months after study initiation, although clinically significantly decreased compared to the control, was statistically marginally significant, a result that may be attributed to our sample size. Because some controversy in this scope still exists, more future studies seem to be necessary. An animal study examined the role of NAC in combination with metformin or NAC alone in non-alcoholic fatty liver disease. After 20 weeks, the mice receiving the combination of NAC and metformin had improved liver function. Although this improvement was seen in both the metformin and NAC groups alone, it was greater in the group receiving both drugs. The combination of NAC and metformin can enhance the treatment of non-alcoholic fatty liver and prevent its progression to non-alcoholic steatohepatitis (28). An open-label multicenter randomized controlled trial compared the effects of NAC and/or ursodeoxycholic acid (UDCA) accompanied by metformin in non-alcoholic steatohepatitis patients. After 48 weeks of treatment, liver function and steatosis degree were improved in all of the study arms; however, ALT levels were statistically significantly decreased only in the NAC + metformin group. This highlights the superiority of NAC over its other conventional peers, and its significant beneficial effects were also seen in the present study (29). Activation of oxidative stress due to different conditions of liver stellate cells and its direct relation to chronic liver injury, hepatic fibrosis, and cirrhosis as the endpoint are important issues. Using antioxidants can minimize oxidative stress and help cure liver cirrhosis. Among the various antioxidants, NAC is a small molecule that has fast access to intracellular compartments by free filtering. In addition to its antioxidant properties, NAC indirectly protects the liver by becoming cysteine, thereby helping to reduce glutathione (30-32). Moreover, NAC serves as a reduced glutathione, nitric oxide (NO), and methyl group donor, indicating methylation of nucleic acids, phospholipids, histones, biogenic amines, and proteins. Furthermore, NAC is a well-known anti-fibrotic agent, because according to the literature, it blocks transforming growth factor-beta (TGF-β) signaling in fibrogenic cells (8). Due to the known mechanisms of NAC as an antioxidant, it can be used in the treatment of fibrosis and liver cirrhosis and, consequently, liver cancer (33). Consistent with other previous studies (29, 34), the currents study did not find any significant NAC effects on hematologic and biochemical parameters. Additionally, as most studies have indicated (27, 29), no serious side

effects were reported during or at the end of the intervention in our study.

Conclusion

The results of this study showed that NAC improved hepatic and renal function by decreasing serum urea and creatinine levels but had no significant effect on hematological and biochemical parameters. NAC also significantly improved the hepatic profile by decreasing ALT, AST, and ALP in the liver enzymes between the intervention and control groups. Moreover, NAC caused a significant decrease in Child-Pugh and MELD scores.

Acknowledgment

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Conflict of interests

The authors declare that they have no conflict of interest.

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