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(Research Article.)

Impact of Pentoxifylline Therapy on the Quality of Life in Nonalcoholic Steatohepatitis Patients

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Abstract: Background: Non-alcoholic steatohepatitis (NASH) is considered an asymptomatic disease. It is well established that NASH decreases patients' health-related quality of life (HRQOL). The HRQOL refers to factors of everyday living that impact medical status. Ten-items domains were selected from short form (SF-36) health survey quality of life which is more related to NASH symptoms, including fatigue, abdominal bloating, and itching, which are negatively affected in almost all aspects of the physical activity of NASH patients. **Objectives:** This study aimed to estimate the effect of pentoxifylline (PTX) treatment on health quality of life in NASH patients by evaluating the SF-36 health questionnaire. **Patients and Methods:** We designed a 6-month, open-labeled clinical trial study for 25 NASH participants. We collected the data from patients at baseline and after 6 months of treatment with PTX at 400 mg three times daily. This questionnaire was performed at Hepatology Clinic, Ain Shams University Hospital. **Results:** The present study showed a marked decrease in SF-36 score concerning fatigue by about (67.16%, p = 0.0001), dizziness (72.28%, p = 0.0001), shortness of breath (15.25%, p = 0.0001), loss of appetite (37.29%, p = 0.0001), legs swelling (13.44%, p = 0.0001), itching (44.44%, p = 0.0001), slurred speech (6.20%, p = 0.0078), abdominal pain (75.86%, p = 0.0001), discoloration of eye and skin (43.20%, p = 0.0001), and abdominal bloating (132.25%, p = 0.0001) after PTX treatment. **Conclusion:** Indeed, after 6 months of treatment, PTX significantly improved the HRQOL in NASH patients compared to baseline.

Keywords: Non-alcoholic steatohepatitis; Health-related quality of life; Pentoxifylline; Fibrosis; liver

1. INTRODUCTION

Non-alcoholic fatty liver (NAFL) can be classified into two categories, firstly, non-alcoholic fatty liver disease (NAFLD), which involves hepatic steatosis, secondly Non-alcoholic steatohepatitis (NASH), which is different from NAFLD by the additional of hepatic cell injury with or without fibrosis [1]. NASH can be triggered by metabolic abnormalities such as diabetes, hypertension, and dyslipidemia, indicating it to be part of a continuity of metabolic etiology. The prevalence of NAFLD globally is about 25%, about 13% in Africa, 23% in Europe, and 32% in the Middle East countries (Egypt) [2]. Despite the widespread prevalence of NAFLD, there is currently no recognized effective therapy for NASH [3]. The progression of NASH disease resulted in the development of hepatic cirrhosis and end-stage liver disease in up to twenty-five percent of NASH patients [4].

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Many NASH patients require a long-term follow-up to determine the progressive disease. It is reported that NASH decreases health-related quality of life (HRQOL)[5]. HRQOL is a multifaceted domain based on the individual perception of their physical, social, and mental domains [6]. There are two basic categories of HRQOL scales: generic and disease-targeted scales [7]. Generic health status scales, like the SF-36 survey, are designed to assess HRQOL concepts relevant to the general population. They enable comparisons between individuals with chronic liver disease and those without such conditions. On the other hand, disease-specific scales for conditions like congestive heart failure, diabetes, and heart disease have shown lower HRQOL in individuals affected by these diseases compared to those without such health issues [8].

Despite NASH's prevalence and clinical complications, no drugs are approved for NASH treatment. A previous study by Koppe et al. reported that pentoxifylline (PTX) plays an essential role in improving NASH disease [9].

Pentoxifylline (PTX), a xanthine derivative and anti-tumor necrosis factor alpha (TNF-α) drug, significantly impacts the molecular and cellular levels. Consequently, previous studies have highlighted the anti-inflammatory, anti-fibrotic, and antioxidant properties of PTX [10]; as a result, it affects the expression of pro-inflammatory genes and the 11th inflammatory cascade. It is well reported that Donate-Correa et al. proved that PTX had renoprotective therapy for patients with diabetic kidney disease represents a new example of drug repositioning [11]. Additionally, Fouda et al. reported that PTX effectively improved hepatic aminotransferases and inflammatory markers in Egyptian NASH patients [12]. Therefore, the effect of PTX treatment on the development of NASH patients quality of life is measured by the SF-36 questionnaire.

2. METHODS

2.1. Patients

This questionnaire was assigned to 25 patients with NASH at baseline and after 6 months of PTX therapy (400 mg three times daily for 6 months) (Survey), As illustrated in (Fig. 1).

It was performed at Hepatology Outpatient Clinic at Ain Shams University. All patients were eligible to:

- **The inclusion criteria:** Patients who have NASH were diagnosed by clinical inspections regarding obesity, abdominal ultrasonography, and elevated liver enzymes. The participants have aged between eighteen and sixty years old in both sexes.
- **The exclusion criteria:** Hepatitis C patients, patients who have had heavy alcohol consumption for more than two years within the last ten years, and patients who have taken drugs known to promote steatosis and renal failure; All participants were assigned on their written informed consent.

The Short Form health questionnaire was used to estimate the quality of life in NASH patients. The SF-36 is widely used in medical and healthcare research to measure subjective health state, including disease-specific and physical categories. The variables were the conception of their physical activity (fatigue, dizziness, shortness of breath, loss of appetite, swelling of legs, itching, slurred speech, abdominal bloating, discoloration of eye and skin, and pain in the upper right abdomen pain). SF-36 was performed at baseline and after 6 months of PTX treatment for all participants. The sample size was calculated using Pass (version 11) Program for sample size calculation, setting power at 90% and α error at 0.05 according to Zein et al., certified by the community, environmental and Occupational Medicine Department Faculty of Medicine, Ain Shams University [13].

2.2. Ethical Approval

The treatment protocol was licensed by Ethical Committee under the regulation of Al-Azhar University, Faculty of Pharmacy (Girls, Cairo) under Certificate no. 312/28 and also approved by IRB of Faculty of Medicine, Ain Shams University certificate no. 13/2022.

2.3. Interpretation of scores

The scale from 1 to 6, with top scores indicating better health. The response to the questionnaire is graded on a scale of 1 to 6 and ranges from “every day” to “none of the time.” Score 1 means every day, score 2 means 4-5 days per week, score 3 means 2-3 days per week, score 4 means 1 day per week, score 5 means less than 1 day, and score 6 means none of the time [14, 15].

2.4. Statistical analysis

Statistical significance differences were performed via GraphPad Prism 8.0.1. Parametric tests were expressed as (Mean ± Standard deviation), while non-parametric tests were introduced as counts and percentages. Parametric data were analyzed with paired Student's t-test. Differences were deemed significant if p-value < 0.05.

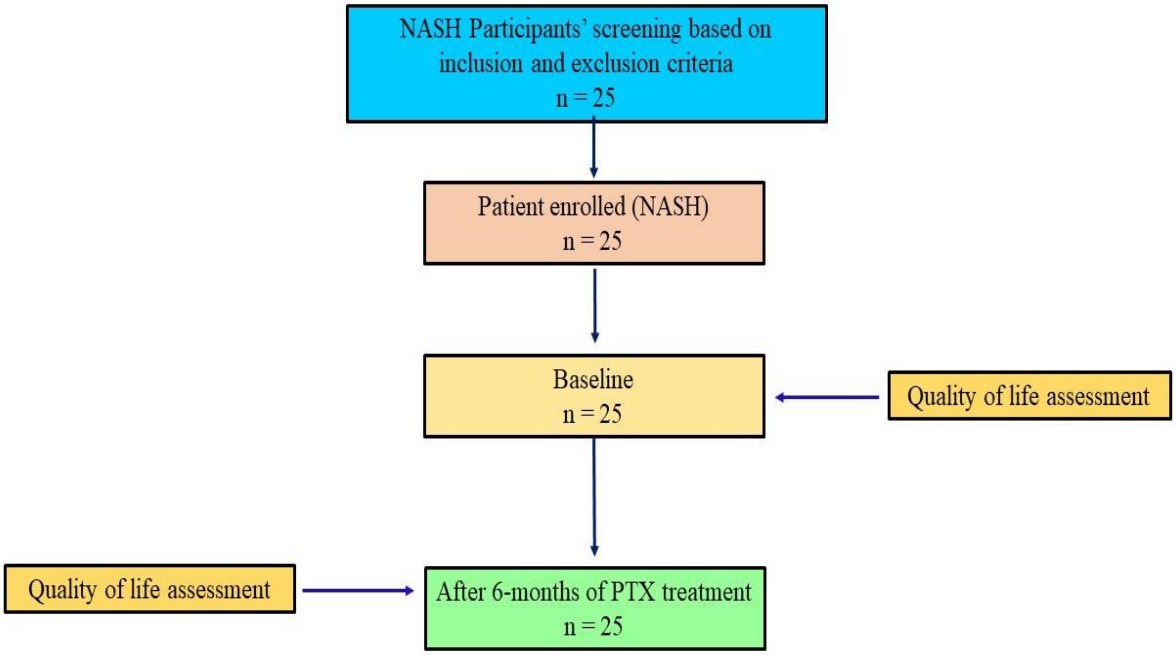

Figure 1. Flow chart of the study

NASH: *Nonalcoholic steatohepatitis;* ***PTX:*** *Pentoxifylline.*

Table 1. Demographics observations for all patients.

Parameters	**At baseline Mean ± SD**	**End of the study Mean ± SD**
Patients	n = 25	
Percentage of male patients	20%	
Percentage of female patients	80%	
Age in years	46.52 ± 8.82 (range 31-60)	
Data (mean ± standard deviation (SD).		

Table 2. Assessment of ten-item SF-36 scores in NASH patients at baseline and the end of the study**.**

Parameters	**Baseline (n=25)**	**End of the study (n=25)**	**p-value**
Fatigue	2.68±1.24	4.48±0.714	< 0.0001#
Dizziness	2.67±1.36	4.60±0.912	< 0.0001#
Shortness of breath	4.72±1.02	5.44±0.650	< 0.0001#
Loss of appetite	3.70±1.30	5.08±1.01	< 0.0001#
Legs swelling	4.76±1.01	5.40±0.866	< 0.0001#
Itching	3.24±1.01	4.68±1.03	< 0.0001#
Slurred speech	5.16±0.943	5.48±0.871	0.0078#
Abdominal pain	2.32±0.802	4.08±0.862	< 0.0001#
Discoloration of eye and skin	3.24±1.01	4.64±0.952	< 0.0001#
Abdominal bloating	1.24±0.435	2.88±1.20	< 0.0001#

Data ***(****mean ± standard deviation (SD)****). Scale 1 to 6, with bigger scores means better health quality of life.*

 # Baseline versus end of the study significant at p-value < 0.05.

3. RESULTS

The demographics data were collected for all subjects at a baseline and after 6 months from the start of PTX treatment. In the current questionnaire, the percentage of male patients was (20%) and female patients (80%). As shown in (Table 1).

To evaluate the influence of PTX in the enhancement of HRQOL on NASH patients, we assessed ten-item SF-36 domains at baseline and after 6 months of PTX therapy, regarding respect fatigue state, dizziness, shortness of breath, loss of appetite, swelling legs, itching, slurred speech, abdominal pain, discoloration of eye and skin, and finally abdominal bloating.

The present study showed significant improvement in all domains when compared to baseline scales. The results are representing as (baseline value) vs. (end of the study), regarding fatigue scale (2.68±1.24) vs. (4.48±0.714) at p = 0.0001, dizziness scale (2.67±1.36) vs. (4.60±0.912) p = 0.0001, shortness of breath (4.72±1.02) vs. (5.44±0.650) p = 0.0001, loss of appetite (3.70±1.30) vs. (5.08±1.01) p = 0.0001, legs swelling (4.76±1.01) vs. (5.40±0.866) p = 0.0001, itching (3.24±1.01) vs. (4.68±1.03) p = 0.0001, slurred speech (5.16±0.943) vs. (5.48±0.871) p = 0.0078, abdominal pain (2.32±0.802) vs. (4.08±0.862) p = 0.0001, discoloration of eye and skin (3.24±1.01) vs. (4.64±0.952) p = 0.0001, and abdominal bloating (1.24±0.435) vs. (2.88±1.20) p = 0.0001. These results are demonstrated in (Table 2).

4. DISCUSSION

Non-alcoholic steatohepatitis is considered a major health problem worldwide. The most serious complications of NASH disease are liver cirrhosis, liver failure, and ending to hepatic cell carcinoma. Comorbidities of disease such as dyslipidemia, diabetes, and cardiovascular disease are considered predisposing factors for the progression of NASH disease [16].

NASH is known as a symptomatic liver illness. We predestined that patients with NASH had deteriorated HRQOL and lower levels of physical and feelings activities at baseline. Consistent with our findings, a previous study found that patients with NASH exhibited a significant decrease in HRQOL across all 10 items compared to the normal population [17, 18].

The use of generic domains, such as the SF-36, provides an accurate and meaningful comparison of HRQOL between healthy and diseased individuals. In this questionnaire, we assessed the effect of PTX therapy on 10 items of SF-36 score regarding physical and psychological domains. This study revealed that treatment with PTX for 6 months improved HRQOL domains. A key strength of our findings is that no prior study had investigated the effect of PTX on HRQOL domains. So, the novelty in our study was the influence of PTX on the life qualities of NASH subjects.

Although NASH is considered an asymptomatic disease, about 50% of subjects with NASH have fatigue which has a noticeable negative influence on all patients. Moreover, patients with progressed hepatic fibrosis because of NASH have characteristic fatigue, as evidenced by a lower value of fatigue score. Fatigue domains were prominent among patients with NASH [19]. Therefore, the fatigue state will improve after taking PTX, which decreases liver fibrosis. In addition, the ten items of the SF-36 domains include symptoms like fatigue, dizziness, shortness of breath, loss of appetite, swollen legs, itching, slurred speech, stomach pain, yellowing of the eyes and skin, and abdominal bloating.

The current survey revealed that administration of PTX for 6 months significantly reduced the 10 items of SF-36 domains of fatigue scale by about (67.16%, p = 0.0001), dizziness (72.28%, p = 0.0001), shortness of breath (15.25%, p = 0.0001), loss of appetite (37.29%, p = 0.0001), legs swelling (13.44%, p = 0.0001), itching (44.44%, p = 0.0001), slurred speech (6.20%, p = 0.0078), abdominal pain (75.86%, p = 0.0001), discoloration of eye and skin (43.20%, p = 0.0001), and abdominal bloating (132.25%, p = 0.0001) after PTX treatment. The improvement in HRQOL in NASH patients could be attributed to free radicals scavengers, anti-inflammatory and antifibrotic properties of PTX therapy [20].

Fatigue is the most prominent symptom documented by NASH illness. However, the underlying molecular mechanisms of fatigue in liver disease such as NASH is still unclear. This could be attributed to changes in neuronal transmission in the central nervous system, which result from poor signaling between liver disease and central nervous system [21]. The liver and peritoneum are richly innervated, carrying afferent signals to the brain in vagal and spinal nerve projections. Activation of these nerves during inflammation in rodents stimulates areas of the brain important in regulating behavioral arousal and results in the development of fatigue-like behaviors. However, patients with recurrent liver inflammation and, therefore after complete hepatic denervation (fibrosis, cirrhosis) often experience fatigue [21]. Furthermore, fatigue is associated with impairment in physical activity.

Our data revealed that PTX treatment for 6 months considerably improved fatigue state and, by extension, health-related quality of life. This

improvement might be attributed to the anti-fibrotic effect of PTX [22]. In addition, prior research has shown that NASH patients often suffer from fatigue and itching [19]. So, the reduction in fatigue leads to a decrease in the itching score.

The most common gastrointestinal symptoms reported by NASH patients include abdominal bloating and abdominal pain [23]. It is well established that there is a direct proportion between irritable bowel syndrome and NASH [23]. Therefore, a decrease in the progression of NASH indicates the enhancement of abdominal bloating and pain.

Our results depicted that administration of PTX for 6 months significantly reduced abdominal pain and bloating compared to baseline. This improvement could be attributed to a decrease in the fluids of the abdominal cavity [24]. Also, previous study reported that PTX decreases the levels of cytokines by its anti-inflammatory effect and could be a novel adjunctive to antispasmodics in relieving abdominal pains in irritable bowel syndrome [25]. Also, attributed to PTX corrected the harmful effects of NASH on the liver. Therefore, any improvement in abdominal pain and bloating enhances the loss of appetite. Regarding to dizziness and swelling of legs, recent study has confirmed the presence of autonomic nervous system dysfunction in those with early stages of NASH.

The presence of autonomic nervous system dysfunction leads to symptoms such as postural dizziness and syncope and is also associated with a number of clinical consequences in hepatic and non-hepatic diseases. portal hypertension occurs when there is increased pressure within the liver's portal vein, which carries blood from the intestines and other organs to the liver. This increased pressure can cause fluid to accumulate in the surrounding tissues, leading to swelling in the legs and ankles, a condition known as Edema [26].

The same improvement was observed in slurred speech and discoloration of the eye and skin because PTX has anti-inflammatory, antioxidant, and anti-fibrotic properties.

5. CONCLUSIONS

NASH patients had a worse quality of life at baseline. We conclude that PTX treatment significantly improves HRQOL in 10 items domains of NASH patients.

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Supplementary Materials: Questionnaire survey on lifestyle of patients with nonalcoholic steatohepatitis

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Conflicts of Interest: The authors declare that there were no conflicts of interest.

Ethical Statement: The treatment protocol was licensed by Ethical Committee under the regulation of Al-Azhar University, Faculty of Pharmacy (Girls, Cairo) under Certificate no. 312/28 and also approved by IRB of Faculty of Medicine, Ain Shams University certificate no. 13/2022.

Author Contribution: Ahmed Abomandour: Conceptualization, Data curation, Writing-Original draft, Formal analysis. Adel Bakr: Methodology, Validation, Investigation, Resources, Reviewing, and Editing. Ahmed ElGhandour: Methodology, Visualization, Reviewing and Editing, Investigation, Resources. Hosny Elewa: Reviewing and Editing. Maha Abdel Rhman: Formal analysis, Reviewing and Editing. Zeinab Zalat: Methodology, Data curation, Reviewing. All authors read and approved the final manuscript. Ahmed Abomandour wrote the first draft of the manuscript, and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

List of Abbreviations:

HRQOL; Health-related quality of life**, SF-36;** Short Form health questionnaire**, NAFLD;** Nonalcoholic fatty liver disease**, NASH;** Nonalcoholic steatohepatitis**, PTX;** Pentoxifylline**, TNF-*α*;** Tumor necrosis factor-alpha**.**

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