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An investigation of tinnitus, noise sensitivity and anxiety levels in liver transplantation patients in the early and late periods: A cross-sectional study

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Abstract

This study aims to evaluate the perception of anxiety, tinnitus, and noise sensitivity in liver transplant patients according to early and late periods following transplantation. The study included 76 patients with liver transplantation. They were divided into two groups according to the duration of time after transplantation: early (1-3 years) and late (5 years or more). A demographic data form, the Tinnitus Handicap Inventory (THI), Weinstein's Noise Sensitivity Scale (WNSS), and the Beck Anxiety Inventory (BAI) were administered and used for data collection. There was a statistically significant difference between the early and late-period groups in terms of WNSS and THI scores ($p<0.05$), whereas there was no statistically significant difference in BAI scores ($p>0.05$). Noise sensitivity and tinnitus perception of the late-period group were statistically higher than those of the early-period group ($p<0.05$). Correlations between BAI, WNSS, and THI scores of late-stage patients were significant ($p<0.05$). A multivariate regression model was performed with the WNSS and the THI as dependent variables. According to this analysis, the THI had a statistically significant positive effect on the BAI in the early period ($p2=0.003$) and WNSS had a statistically significant positive effect on the BAI score in the late period ($p2=0.002$). Both otologic and psychological effects are observed in patients with liver transplantation. The post-transplant period triggered otologic symptoms more. It is also noteworthy that psychological and otologic symptoms are in correlation. Psychological and otologic evaluations with a multidisciplinary approach should gain importance in the post-transplant period.

Keywords: Liver transplantation, tinnitus, anxiety, noise sensitivity, early-late stage

Introduction

Organ transplantation is an important therapeutic option for many diseases. Liver transplantation is a life-saving intervention for individuals with incurable, progressive, and irreversible liver disease and it is a radical method to improve quality of life [1]. Liver-related diseases lead to a deterioration in quality of life by negatively affecting various domains such as self-sufficiency, family and friend relationships, work life, and plans for the future. In addition, various factors such as the seriousness of the disease or organ rejection during the pre-transplant evaluation phase also cause psychosocial stress in the patient [2]. In addition, transplant recipients may develop many psychological distresses, such as a sense of obligation towards the donor, clinicians, and family members [3,4]. Akbulut et al. examined liver transplant patients grouped according to different characteristics in terms of anxiety, depression, and self-care skills. They obtained high anxiety scores in all groups [5]. Similarly, in a study

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analyzing liver transplant patients psychologically, 29.7% of 64 transplanted patients were anxious and 57.8% were depressed [2]. In the post-transplant period, factors that cause hearing loss, such as side effects of immunosuppressants or ototoxic drugs, and the emergence of tinnitus also cause depression and anxiety [6,7]. Hearing loss, the prevalence of which increases with age, is a common disorder, and the use of ototoxic drugs is a risk factor for hearing loss. Liver transplantation, which has recently become a standard procedure, is associated with side effects. When the side effects of immunosuppressants used after transplantation are investigated, hearing loss cases draw attention [8]. However, little is known about cochlear involvement in post-transplant patients [7]. Limited studies have reported hearing loss associated with different calcineurin inhibitors (CNIs) after organ transplantation [8-10]. Rifai et al. [8] suggested that hearing loss in liver transplant patients was positively associated with tacrolimus immunosuppression. They reported that calcineurin inhibitor-related neurotoxicity is a possible mechanism for hearing loss. In another study, all patients were retrospectively analyzed for hearing loss after liver transplantation. Although 25 out of 521 transplanted patients (5%) used hearing aids, approximately 50% of the patients needed hearing aids within 2 years after transplantation. In the same study, 16 patients with severe hearing loss after transplantation were reported. They also reported that 9 of these 16 patients had tinnitus (56%) and 3 had ear pain (19%) [11]. There are also a few case reports [12-14] of the occurrence of otologic symptoms after organ transplantation. Impaired hearing health is a common condition that can seriously affect a person's quality of life. Krog et al. stated that individuals with tinnitus have significantly more anxiety and depression than individuals without tinnitus [6]. There is no study in the literature that examines and compares liver transplant patients otologically in the early and late periods. This study aimed to evaluate anxiety, tinnitus, and noise sensitivity perception of liver transplant patients according to post-transplantation periods.

Material and Methods

Research design

In this study, a complementary cross-sectional design was used to obtain information about anxiety, tinnitus, and noise sensitivity perception in liver transplant patients according to years after transplantation.

Participants

The sample of this study was determined by power analysis. According to the calculation made using the G*power 3.1 program; The sample size was determined as 70 (35 per group) with an effect size of 0.96, margin of error of 0.05, a confidence level of 0.95, and a population representation of 0.95 [15]. The study included 100 liver transplant patients and was conducted at the largest Liver Transplant Institute in Turkey. Ten patients were excluded from the study because they were previously diagnosed with otologic problems, 9 patients were transplanted for the second time, and 5 patients did not want to continue with the subjective measurements. As a result, the study was completed with 76 patients. Among liver transplant recipients, those who had undergone liver transplantation between 1 and 3 years after transplantation were categorized as “early stage” and those who had undergone liver transplantation for more than 5 years were categorized as “late stage”. The study included 36 patients in the early period and 40 patients in the late period. Patients with otologic symptoms such as hearing loss, tinnitus, and noise sensitivity before transplantation and those who used ototoxic drugs (such as aminoglycoside antibiotics, loop diuretics, and salicylates), and those with renal failure, arterial hypertension, and DM were excluded from the study. 'The diagram of the participants included in the study in the study proccess is shown in Figure 1.'

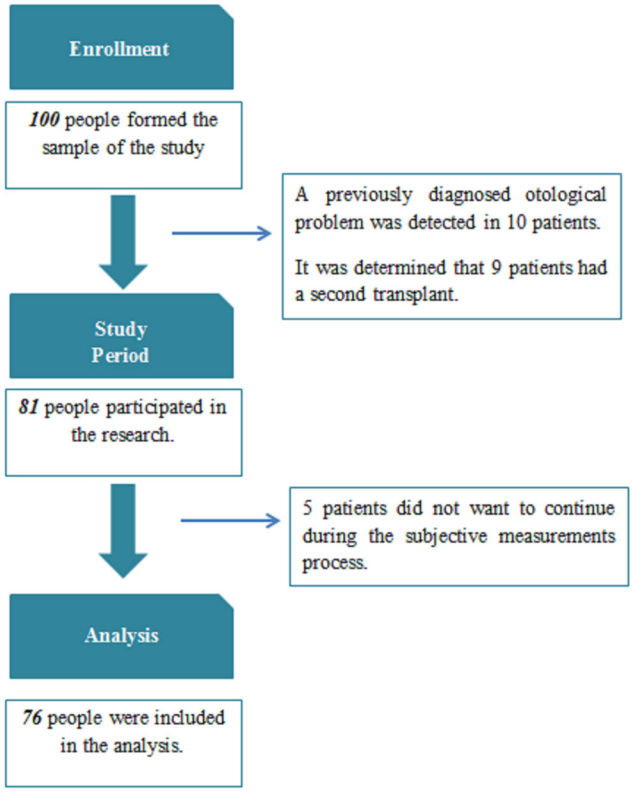

Figure 1. Diagram of the participants included in the study

Data collection

Study data were collected between March 2022 and June 2022 via face-to-face interviews. A demographic data form, the Tinnitus Handicap Inventory (THI), Weinstein's Noise Sensitivity Scale (WNSS), and the Beck Anxiety Inventory (BAI) were read to the patients by the researchers and they were answered by each patient.

Data collection tools

BAI is a scale differentiates between anxiety and depression and assesses adults with anxiety disorders. This scale contains 21 self-report items, and evaluates symptoms such as anxiety, dizziness, and worry with a classification from normal to severe.

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The scale consists of 21 items and is scored between 0 and 3 in a 4-point Likert format. Scoring ranges were determined at low (8 to 15 points), medium (16-25 points), and high (26-63 points) [16,17].

WNSS is a 21-item Likert-type scale used to assess individuals' noise sensitivity, with each item responded to by agreeing or disagreeing in a varying degree between 1 and 6. The scores corresponding to the answers to each item are summed and the score is calculated. The cut-off points of the lowest and highest scoring 1/3 of the sample group are considered as cut-off points and are evaluated as "noise sensitive" or "not noise sensitive" according to these groups. The scale was designed by Weinstein, and it was translated into Turkish and its validity and reliability study was conducted by Keskin et al. [18,19].

The THI was developed by Newman et al. and its adaptation and validity and reliability study into Turkish was conducted by Aksoy et al. The scale, which evaluates the distress and dysfunction caused by tinnitus in the individual and has functional, emotional, and catastrophic sub-dimensions, consists of 25 items scored with a score of "4" for "yes", "2" for "sometimes", and "0" for "no". The maximum score that can be obtained from the scale is 100. The first of the 3 subscales, the functional subscale, which consists of 12 questions, shows the limitation in the mental, social/occupational, and physical functions of the individual. The highest score that can be obtained from the functional subscale is 48. The second of the 3 subscales, the emotional subscale, shows the individual's emotional reactions to tinnitus and the highest score that can be obtained from the emotional subscale is 32. The last of the 3 subscales is the catastrophic subscale and consists of five items. The highest score that can be obtained from the catastrophic subscale is 20 [20,21].

Ethical principles of research

Approval was obtained from the Non-Interventional Clinical Research Ethics Committee of the Institute of Health Sciences of a university (decision number: 2021/2251). All individuals volunteered to participate in the study.

Statistical analysis

Data analysis was carried out with SPSS (Statistical Program in Social Sciences) 25 program. Whether the data showed normal distribution or not was analyzed with the Kolmogorov Smirnow Test. The Kolmogorov Smirnov Test was used to check whether the data fit the normal distribution. The significance level (p) was taken as 0.05 for comparison tests. Parametric test method was used because the data showed normal distribution ($p>0.05$). In independent paired groups, comparisons were made with the significance test of the difference between two means (t test). Pearson correlation coefficient was used to test the relationship between variables. The relationship between the dependent variable and the independent variables in the data was evaluated by multivariate linear regression analysis. Chi-square ($\chi 2$) analysis was used in the evaluation of categorical data. Cronbach α coefficient was used to determine the reliability analysis of the scales.

Results

No statistically significant difference was found between the groups according to age and gender ($p>0.05$, Table 1). The groups were homogeneously distributed according to age and gender variables.

There was no statistically significant difference between the groups in the BAI score ($p>0.05$). The WNSS score was statistically lower in the early period group compared to the late period group ($p<0.05$). In addition, the THI score was statistically lower in the early period group compared to the late period group ($p<0.05$, Table 2).

In the early post-transplant period, there was a statistically significant positive relationship between BAI and THI scores at a moderate level ($r=0.526$) ($p=0.001<0.05$, Table 3). If the BAI score increases, the THI score will increase, and vice versa. In addition, there was a statistically significant relationship between BAI and WNSS scores in the late post-transplant period ($p=0.001<0.05$, Table 3). If the BAI score increases, the WNSS score will increase, and vice versa.

Table 1. Comparisons according to demographic variables

Variable	Group	Transplant date		Total	p value
		Early period	Late period		
		n (%)			
Sex	Female	13 (36.1%)	16 (40%)	29 (38.2%)	0.727[a]
	Male	23 (63.9%)	24 (60%)	47 (61.8%)	
	Total	36 (100%)	40 (100%)	76 (100%)	
		Early period n=36	Late period n=40		
		Min±SD (Min-Max)			
Age		44.81±12.25 (19-58)	45.71±10.35 (21-58)		0.731[b]

n: sample number, %: percentage, p[a]: Chi-square test value ($\chi 2$), SD: standard deviation, p[b]: Mann Whitney U test, p value, *$p<0.05$; there is a statistically significant difference between the groups

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Table 2. Comparisons according to scale scores

Value	Early period (n=36)		Late period (n=40)		p value
	Mean±SD	Cronbach α	Mean±SD	Cronbach α	
BAI	6.31±5.04	0.713	8.78±7.92	0.885	0.113
WNSS	64.78±27.25	0.919	80.63±28.84	0.936	**0.016***
THI	2.94±10.95	0.958	8.23±9.71	0.853	**0.029***

SD: standard deviation, p Value: t test significance value, *p<0.05: there is a statistically significant difference between the groups

Table 3. Correlation between scale scores between groups

Variables	Value	Early period			Late period		
		BAI	WNSS	THI	BAI	WNSS	THI
Time after transplant	R	-0.160	-0.090	0.073	-0.211	-0.022	-0.236
	P	0.351	0.603	0.674	0.191	0.892	0.142
BAI	R		0.280	**0.526**		**0.503**	0.186
	P		0.098	**0.001***		**0.001***	0.250
WNSS	R			0.287			0.170
	P			0.090			0.293

r: pearson correlation coefficient, p value: statistical significance, *p<0.05: there is a statistically significant relationship between the groups

In the multivariate regression model in which WNSS and THI scores were independent variables and the BAI score was the dependent variable, the THI score had a statistically significant positive effect on the BAI score (p2=0.003<0.05, Table 4). The WNSS score had no statistically significant effect on the BAI score (p2=0.363>0.05, Table 4). If the THI score increases by 1 unit, the BAI score increases by 0.223 points (β1=0.223, p2=0.003<0.05, Table 4). THI score explains 25.2% of the BAI score (R2=0.252, p1=0.003<0.05, Table 4).

In the multivariate regression model in which WNSS and THI scores were independent variables and the BAI score was the dependent variable, it was found that the WNSS score had a statistically significant positive effect on the BAI score (p2=0.002<0.05, Table 4). THI score had no statistically significant effect on the BAI score (p2=0.475>0.05, Table 4). If the WNSS score increases by 1 unit, the BAI score increases by 0.133 points (β1=0.133, p2=0.002<0.05, Table 4). The WNSS score explains 22.4% of the BAI score (R2=0.224, p1=0.002<0.05, Table 4).

Table 4. Regression analysis of the BAI with WNSS and the THI

Group	Dependent	Independent	R^2	F test	p1 value	β1	t Test	p_2 value
Early period	BAI	Constant	0.252	6.908	0.003*	**3.963**	**2.064**	**0.047***
		WNSS				0.026	0.922	0.363
		THI				**0.223**	**3.185**	**0.003***
Late period	BAI	Constant	0.224	6.628	0.003*	-2.672	-0.800	0.429
		WNSS				**0.133**	**3.394**	**0.002***
		THI				0.084	0.722	0.475

R2: explanatory coefficient, **p1<0.05: F test result for model significance, β1: unstandardized regression coefficients, *p2<0.05: t test result for regression coefficients significance

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Discussion

Organ transplantation is one of the most important therapeutic innovations in medicine. The success of an organ transplant depends on the cooperation and harmonious work of a team of various medical specialties [22]. As the number of survivors after transplantation increases, the problems experienced by patients in different branches also increase. Psychological and otologic effects, which have an important place among these problems, draw attention. The aim of our study was to subjectively evaluate the psychological and otologic effects on patients according to the time elapsed after liver transplantation.

Among liver transplant candidates, 19%-55% anxiety symptom levels and 17%-62% depression symptoms levels have been reported [23]. In a study of 127 post-transplant patients, 23% of all patients showed persistent anxiety symptoms and 29% of all patients showed persistent depression symptoms until 2 years later [24]. On the contrary, Moore et al. [25] reported that pre-existing depression and anxiety levels and other negative mood states decreased 1 year after transplantation, even if the symptoms were not of clinical severity. In another study, it was suggested that patients' anxiety levels decreased with the effect of psychological support [26]. In our study, there was no statistically significant difference in BAI scores between the groups, but the fact that BAI scores in the late period group were higher than those in the early period group suggests that the level of anxiety may increase as the time after transplantation passes. Many factors such as time after liver transplantation, immunosuppressive drugs, adaptation to restrictive lifestyle rules, negative impact on quality of life, coping style with stress, and family environment may be effective in the difference between the studies in the literature [27-29]. In addition, the relationship between otologic symptoms and psychological symptoms in transplant patients obtained in our study should not be forgotten. Our study showed that anxiety levels were positively associated with tinnitus complaints in the early period group and anxiety levels were positively associated with noise sensitivity in the late period group. The relationship between tinnitus and anxiety can be explained by the involvement of the limbic system in the pathophysiology of tinnitus. Studies have reported that individuals with tinnitus have reduced gray matter density in the subcallosal area associated with the limbic system [30]. Jastreboff explained the tinnitus mechanism in 1990 in relation to the limbic system and the autonomic nervous system under the name of the neuropsychological model [31]. In this mechanism, the perception of anxiety, depression and tinnitus has a positive relationship. In the presence of tinnitus, the stimuli transmitted to the limbic structures via the amygdala cause negative emotional expressions [30,31]. This mechanism mentioned in the literature supports the relationship between anxiety and tinnitus that we found in our study.

Tinnitus is among the most commonly reported symptoms after liver transplantation [8,32]. Post-transplant immunosuppressive treatment protocols often include drugs such as mycophenolate, tacrolimus, sirolimus, and steroids [22].

Hizal et al. [22] stated that kidney and liver transplant recipients develop different otological problems in the early and late stages. Rifai et al. [11] confirmed the reported high incidence of hearing loss in adults after liver transplantation with objective audiometric data. In addition, they found pathologic hearing test results in many patients with no perception of hearing problems. In another study, in 521 patients who underwent transplantation, 16 patients who developed severe hearing loss in the post-transplant period were identified. It was reported that 56% of these patients had tinnitus, 19% had ear pain, and 25% had a history of sudden hearing loss. The incidence of cochlear involvement in the post-liver transplant period was found to be high. Most of the patients who experienced hearing loss in the post-transplant period had bilateral hearing loss. It draws attention to a toxicity related to the dose of drugs used in the post-transplant period [7]. Many of the patients in our study were taking immunosuppressive drugs. Such immunosuppressive drugs are also known to cause otologic symptoms such as tinnitus [33]. In addition, the fact that the incidence of both tinnitus and sensitivity to noise was higher in the late period patients in our study compared to the early period supports the effect of long-term immunosuppressive drugs on tinnitus.

In a population-based, prospective study with 9.842 participants, Beutel et al. reported that anxiety and depression symptoms were triggered over time in participants who experienced noise sensitivity [34]. In our study, otologic symptoms of transplant patients were evaluated at the perceptual level using subjective inventories. The high tinnitus and noise sensitivity scores and the correlation between anxiety and tinnitus and noise sensitivity in subjective evaluations support the objective evaluations in the literature. In addition, it contributed to the literature by examining the relationship between the otologic symptoms of transplant patients and both their perceptual evaluations and psychological effects.

Conclusions

In conclusion, our study subjectively supports that otologic symptoms can be seen frequently after liver transplantation. In addition, it is seen that patients have psychological effects in the post-transplant process and this effect is also related to otologic symptoms. We think that a multidisciplinary approach to liver transplantation patients in the post-transplantation period is important to positively affect the quality of life.

Limitations

The limitation of the study is that these data could not be confirmed with objective hearing tests and cross-checking could not be performed. In future studies, we think that psychological and otologic evaluations before and after transplantation will better explain both the effect of transplantation on these symptoms and the cause-effect relationship of these symptoms.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The study was approved by the Inonu University Non-Interventional Clinical Research Ethics Committee of the Institute of Health Sciences (decision number: 2021/2251).

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