Original Article

J Babol Univ Med Sci
Vol 20, Issu 8; Aug 2018. P:15-24

An Investigation of the Effect of Green Tea on Liver Enzymes and Serum Lipid Profiles in Patients with Beta–Thalassemia Major

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J Babol Univ Med Sci; 20(8); Aug 2018; PP: 15-24

Received: Oct 15th 2017, Revised: Feb 17th 2018, Accepted: Mar 26th 2018.

ABSTRACT

BACKGROUND AND OBJECTIVE: In patients with beta – thalassemia major, iron overload and oxidative stress cause metabolic disorders, especially in the liver. Green tea may be beneficial in reducing the complications of this disease due to the iron chelation and antioxidant properties. Therefore, this study was conducted to evaluate the effect of green tea on liver enzymes and serum lipid profiles in these patients.

METHODS: This randomized clinical trial was performed on 52 patients with beta – thalassemia major in two groups of controls and intervention (26 people in each group). Patients in the intervention group received 3 cups of green tea for 8 weeks and the control group consumed the same amount of boiled water each day for the same period. The assessment of dietary intake, AST and ALT, total cholesterol, triglyceride, LDL-C and HDL-C, and height and weight measurements were performed at the beginning and the end of the study.

FINDINGS: Significant decrease in the levels of ALT enzymes ($p<0.0001$, 38.8±4.8 U/L) and AST ($p<0.007$, 39.53±11.01 U/L) and serum triglyceride ($p<0.0001$, 135.03±31.82 mg/dl) compared to baseline values (42.53±5.26 U/L, 43.46±9.7 U/L, 150.35±33.34 mg/dl) was observed in the green tea group. The consumption of green tea resulted in a significant reduction in total serum cholesterol levels at the end of the study in the intervention group compared with the control group ($p=0.006$).

CONCLUSION: The results of this study showed that green tea consumption reduced levels of liver enzymes, triglycerides and especially total serum cholesterol in patients with beta – thalassemia major.

KEY WORDS: *Green tea, Alanine aminotransferase, Aspartate aminotransferase, Serum cholesterol, Triglyceride, Beta – thalassemia major.*

Please cite this article as follows:

Rafraf M, Haghravan S, Soeizi E, Asghari-Jafarabadi M. An Investigation of the Effect of Green Tea on Liver Enzymes and Serum Lipid Profiles in Patients with Beta–Thalassemia Major. J Babol Univ Med Sci. 2018;20(8):15-24.

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[DOR: 20.1001.1.15614107.1397.20.8.2.4]

[DOI: 10.18869/acadpub.jbums.20.8.15]

Introduction

Beta – thalassemia major is a disease caused by the lack or severe reduction in beta-globin chain synthesis following gene mutation. This results in the production of a large number of alpha-globin chains that are not capable of producing tetramer hemoglobin (1). Thalassemia is the most common genetic disease in the world and nearly 200 million people in the world are affected by thalassemia syndromes (2). In the world, there is a thalassemia belt stretching from southern Europe and northern Africa to the Middle East and the Far East, and Iran is also on it (3).

Iran is one of the main centers of β – thalassemia prevalence and is expected that from two to three million carriers of β – thalassemia and 25,000 patients with β – thalassemia live in Iran (4). In the clinical presentation of patients with β – thalassemia major, various problems such as ineffective hematopoiesis, unbalanced accumulation of globin subunits in red blood cells and chronic hemolysis are observed (2). In cases of iron overload and an imbalance between oxidant and antioxidant, metabolic disorders first involve liver and spleen. With iron overload in the liver, free radicals and lipid peroxidation products cause inflammation, fibrosis, and, eventually, death of liver cells (5).

After liver damage in these patients, the levels of liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) increase in serum (6). Changes in serum lipids have been associated with anemia, increased activity of the macrophage system, and liver function failure (7). Today, Desferrioxamine (DFO), Deferiprone (DFP), and Deferasirox (DFX) are used as iron chelators to treat iron overload in patients with thalassemia. Research results show that several compounds, such as 2,3-dihydroxybenzoic acid (DHB), curcumin, and especially green tea catechins, have the potential for iron chelating activity in iron overload conditions (8 – 11).

Green tea contains the highest amount of flavonoids compared with black tea and oolong tea (12). Important flavonoids (80% to 90%) that are present in green tea include catechins (flavan-2-ols) such as epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC) and epigallocatechin-3-galate (EGCG), the highest of which is EGCG (48 – 55%) (13). Moreover, in a study on rats with fatty liver, Parka et al. reported that the green tea extract reduced the serum levels of ALT and lipids in the liver cells by 1% (14). Studies on animal models have shown that green tea has beneficial effects, including reducing liver enzymes, improving lipid profile, and reducing serum levels of total cholesterol and LDL-C (14, 15). With its iron chelating properties, green tea can eliminate oxidative effects in the liver cells (8, 11).

Augustyniak et al. showed that green tea and ethanol consumption reduced the oxidation of fat, and ALT and AST enzymes (16). The results of the study by Usama indicated a decrease in the levels of AST, ALT, total cholesterol and triglyceride, LDL-C and VLDL (17). In addition, Tadayon et al. showed that the mean total cholesterol in the green tea group decreased significantly after four weeks. Triglyceride and serum LDL-C were also significantly reduced in the green tea group compared to the control group, but no significant changes were observed in HDL-C between the control and intervention groups (18).

Considering the importance of β – thalassemia and its prevalence in Iran, and considering the fact that so far, there has been no study on the effects of green tea on target indices of the present study in patients with thalassemia, conducting studies about auxiliary strategies to control its side effects seems necessary. Given the fact that iron overload and oxidative stress are in the pathology of the disease and given that green tea may be effective in controlling this disease due to its iron chelating properties and antioxidants, the present study was aimed at determining the effects of green tea consumption on liver enzymes and serum lipid profiles in patients with thalassemia major, and was designed to provide appropriate approaches to reduce the complications of this disease.

Methods

This randomized controlled clinical trial was first approved by the Ethics Committee of Tabriz University of Medical Sciences and registered in the clinical trial system (IRCT: 201403303664 N 10), and was carried out among patients with β – thalassemia major referring to Shahid Ghazi Tabatabai Hospital, Tabriz University of Medical Sciences.

The present study is part of a larger study. Patients with β–thalassemia major, above 18 years of age, iron-chelating therapy with deferoxamine and absence of hepatitis B and C were enrolled. The sample size was calculated to be 22 patients according to the iron index based on the study of Kassab – Chekir et al. (19), with a 95% confidence interval and 80% power and a two-sequence test using the Pocock's sample size formula. Finally, the final volume of the required sample with a 20% chance of dropping was found to be 52 persons

[DOR: 20.1001.1.15614107.1397.20.8.2.4]
[DOI: 10.18869/acadpub.jbums.20.8.15]

who were randomly divided into two groups of intervention (receiving green tea [n = 26]) and control (receiving boiled water [n=26]).

Eligible patients from Shaheed Ghazi Tabatabaei Hospital, who referred monthly for blood transfusion and follow-up therapy, were selected by random convenience sampling. If patients had the necessary inclusion criteria for entering the study, and if they were willing to enter the project, informed written consent was obtained from them. Patients were those who had a medical history of β–thalassemia major since their childhood. Diagnosis of β–thalassemia major in childhood is based on severe anemia, with signs of ineffective erythropoiesis such as enlargement of the liver and spleen, severe microcytosis, and increased HbF, HbA2 levels.

Many patients need long-term transfusion therapy to keep their hematocrit at least in the range of 27–30%. Furthermore, in infants with β – thalassemia major, Hb levels reach less than 5 g/dL, indirect bilirubin increases, and eventually with iron accumulation, serum ferritin levels will increase (20). Patients in both groups were matched in terms of age, gender, and body mass index (BMI). Before the study, the subject of the research was explained to the patients and written consent was received. Then, for collecting general information, a personal information questionnaire was prepared. In order to evaluate the dietary intake, a 3–day diet record (including 2 normal days and 1 day off) was collected before intervention and at the end of the intervention (week 8).

Dietary record data were analyzed using Nutritionist 4 application (First Databank Inc., San Bruno, CA). Anthropometric measurements (including weight and height) were performed at the beginning and at the end of the study, and the BMI was calculated by dividing weight in kilograms by height in meters squared. The intervention group received three cups of green tea daily (in the form of a bag made by the Institute of Medicinal Plants, Jahad University, Karaj, Iran) immediately after eating food (breakfast, lunch and dinner) for eight weeks, and the same amount of boiled water was recommended for a similar period and the same method for control group.

Making green tea: Subjects placed each 2.5 gram green tea bag in a lidded glass of 150 cc boiling water, placed the lid and drank the tea after 12 minutes. The packs containing green tea bags were delivered to the patients every two weeks and in order to estimate the follow-up of the participants, subjects were requested to deliver the packs to count the remaining bags. Patients were asked to not change their diet and physical activity during the study as far as possible, and if there were any changes, they had to notify the researcher. The fasting blood samples (12–14 hours) were collected before and after the intervention.

The measurement of liver enzymes (ALT and AST) was performed on the basis of IFCC using an enzyme spectrophotometer by means of an autolyser (Abbot, Model Alcyon300, USA) and using the Pars Azmoon kit (CHOD–PAP). The aminotransferase enzyme catalyzes the transfer of amine from alanine to 2-oxoglutarate, which leads to the formation of pyruvate and glutamate. The catalytic concentration was determined as NADH reduction at 340 nm wavelength by the reaction of lactate dehydrogenase. Total cholesterol, triglyceride and HDL-C were also measured by an enzyme spectrophotometer using an autolyser and using the Pars Azmoon kit. The LDL-C measurement was calculated by Friedewald equation:

$$\textbf{LDL–C (mg/dl) = TC–(HDL+TG/5)}$$

In this study, SPSS (Version 16.) was used for statistical analysis. Chi-square test was used to compare qualitative variables between intervention and control groups before intervention.

Independent t-test was used for comparing quantitative variables between the two intervention and control groups before intervention. Paired t-test was used to compare the changes of quantitative variables before and after the intervention in each group and covariance test was used for comparing the quantitative variables between the two groups after the intervention by modifying baseline levels and confounding variables. The percentage changes were calculated using the following formula, and $p < 0.05$ was considered statistically significant.

$$\frac{\text{Variable level (after intervention- before intervention)}}{\text{Variable level before intervention}\times 100} = \text{Percentage changes}$$

Results

The mean age of the subjects in the green tea group was 23.15±3.33 and in the control group was 24.3±23.15 years. Moreover, the mean deferoxamine intake in the green tea group was 31.3±53.39 and in the control group was 33.07±4.26 mg/kg (Table 1). There

[DOR: 20.1001.1.15614107.1397.20.8.2.4]
[DOI: 10.18869/acadpub.jbums.20.8.15]

was no significant difference between the two groups in terms of mean age and gender distribution, marital status and education, and the rate of drug intake (Table 2). In both groups, the mean BMI of subjects was within the normal range before and after intervention. There was no statistically significant difference between the two groups in any anthropometric indices at the beginning and the end of the study. There was no significant change in the anthropometric indices after intervention in any of the groups.

The average energy and macronutrients intake before the intervention and at the end of the study did not differ significantly between the two groups. At the end of the study, there was no significant change in the mean of receiving these variables compared to the beginning of intervention in any of the groups (Table 3). There was no significant difference between the mean levels of ALT (42.5±53.26 U/L) and AST (46.16±84.14 U/L) in the baseline before the study. Based on the findings of the covariance analysis, after adjusting the confounder of the initial values and other confounding factors, including deferoxamine intake, changes in weight and energy in terms of serum ALT and AST after intervention were not significantly different between the two groups (Table 4).

The mean of lipid profile variables was not significantly different from baseline before the intervention. Based on the findings of the covariance analysis, there was no statistically significant difference between the two groups in terms of serum triglyceride, LDL-C and HDL-C after modification of the confounder of the initial values and other confounding factors, such as deferoxamine intake, changes in body weight and energy intake (Table 5).

However, the mean serum cholesterol level was significantly different between the two groups after the intervention (180.56±92.40 mg/dl in the green tea group and 173.47±07.94 mg/dl in the control group) ($p<0.05$).

Table 1. General characteristics of patients with β – thalassemia major in the two groups of intervention and control

Variables	Group	Green tea N(%)	Control N(%)	P-value
Gender	Male	15(57.7)	12(46.2)	≠ 0.67
	Female	11(42.3)	14(53.8)	
Marital status	Married	8(30.76)	5(19.23)	≠ 0.75
	Single	18(69.23)	21(80.76)	
Education	Illiterate	3(11.53)	2(7.69)	≠ 0.95
	Below high school diploma	5(19.23)	4(15.38)	
	High school diploma	6(23.07)	9(34.61)	
	University degree	12(46.15)	11(42.3)	

*Independent t-test, ≠ Chi-Square

Table 2. Comparison of the mean anthropometric indices in the two groups before and after the intervention

Variables	Group	Green tea Mean±SD	Control Mean±SD	P-value
Height (cm)		5.157±51.92	6.160±39.15	* 0.34
Weight (kg)	Beginning of study	5.52±08.08	5.51±47.70	
	End of study	5.51±44.08	5.51±49.72	* 0.64
	P-value +	+ 0.28	+ 0.87	
BMI (kg/m^2)	Beginning of study	1.20±93.90	1.19±73.42	
	End of study	20±2.78	1.19±62.42	* 0.33
	P-value +	+ 0.25	+ 0.1	

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Table 3. Comparison of energy and macronutrients intake in the two groups before and after the intervention

Variables	Group	Green tea Mean±SD	Control Mean±SD	P-value
Calories (kcal/day)	Beginning of study	192.1838±8	196.1884±60	* 0.586
	End of study	502.1713±6	237.1716±5.2	
	P-value +	+ 0.13	+ 0.6	
Carbohydrate (gr/day)	Beginning of study	47.259±3.7	25.75±81.58	* 0.950
	End of study	95.232±5.2	16.72±17.02	
	P-value +	+ 0.5	+ 0.39	
Protein (gr/day)	Beginning of study	26.77±1.3	25.75±81.58	* 0.721
	End of study	72±25.5	16.72±17.02	
	P-value +	+ 0.5	+ 0.39	
Fat (gr/day)	Beginning of study	20.54±1.5	21.55±07.39	* 0.913
	End of study	16.54±8.9	12.54±76.08	
	P-value +	+ 0.9	+ 0.8	

*** Independent t test + Paired t test**

Table 4. Comparison of levels of liver enzymes in the two groups before and after intervention

Variables	Group	Green tea Mean±SD	Control Mean±SD	P-value
Serum ALT (U/L)	Beginning of study	42.5±53.26	46.16±84.14	* 0.2 ≠ 0.5
	End of study	38.4±8.8	44.18±17.2	
	P-value +	+ 0.0001	+ 0.007	
Serum AST (U/L)	Beginning of study	43.9±46.7	47.11±03.05	* 0.3 ≠ 0.91
	End of study	39.11±53.01	43.13±03.10	
	P-value +	+ 0.0001	+ 0.001	

ALT: alanine aminotransferase AST: aspartate aminotransferase * Independent t test + Paired t test ≠ ANCOVA

Table 5. Comparison of serum lipid levels in the two groups before and after intervention

Variables	Group	Green tea Mean±SD	Control Mean±SD	P-value
Serum cholesterol (mg/dl)	Beginning of study	57.205±19.38	38.178±49.19	* 0.5 ≠ 0.006
	End of study	56.180±40.92	47.173±94.07	
	P-value +	+ 0.0001	+ 0.11	
Serum triglyceride (mg/dl)	Beginning of study	33.150±34.34	40.138±9.50	* 0.5 ≠ 0.06
	End of study	31.135±82.03	34.133±2	
	P-value +	+ 0.0001	+ 0.82	
Serum LDL-C (mg/dl)	Beginning of study	14.62±20.20	11.64±60.80	* 0.93 ≠ 0.07
	End of study	13.57±60.15	20.62±11.53	
	P-value +	+ 0.0001	+ 0.05	
Serum HDL-C (mg/dl)	Beginning of study	5.44±65.73	5.45±65.53	* 0.7 ≠ 0.2
	End of study	8.43±29	5.41±41.92	
	P-value +	+ 0.15	+ 0.0001	

ALT: alanine aminotransferase AST: aspartate aminotransferase * Independent t test + Paired t test ≠ ANCOVA

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In the green tea group, a significant decrease of 8.77% and 9.04% was observed in serum ALT and AST levels, respectively, whereas in the control group, the levels of serum ALT and AST decreased significantly by 6.32% and 8.51%, respectively, compared with baseline values (Fig. 1).

Green tea consumption significantly reduced serum cholesterol levels by 11.91%, serum triglycerides by 10.18%, and serum LDL-C by 8.12% compared to baseline, but changes in HDL-C was not significant. In the control group, the significant reduction of HDL-C was found to be 7.93% higher than the baseline values, but the percentage change for other parameters was not significant (Fig. 2).

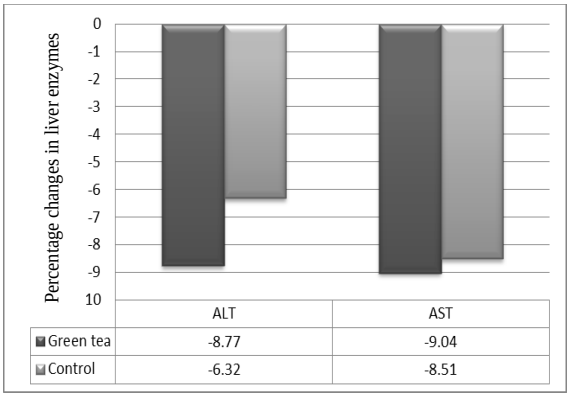

Figure 1. Percentage changes in variables of liver enzymes (ALT and AST) in the two green tea and control groups

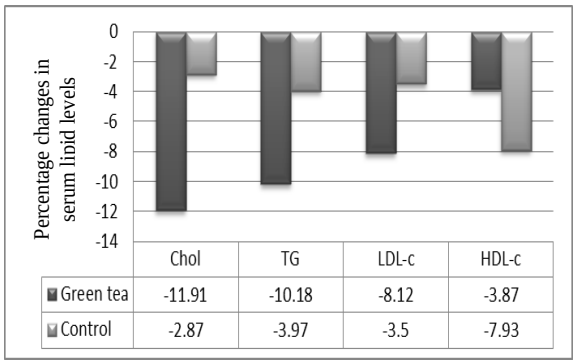

Figure 2. Percentage changes in serum lipid levels in two groups of green tea and control; changes were not significant for other parameters

Discussion

The results of our study showed that green tea consumption in β – thalassemia major patients during 8 weeks resulted in a significant decrease in total serum cholesterol, triglyceride and LDL-C levels compared to the beginning of the study, and only the reduction of total serum cholesterol compared to the control group was significant. In our study, the mean total serum cholesterol level in the green tea group was higher than the normal range at baseline. In addition, mean levels of serum triglyceride in the green tea group were higher than normal range. Serum lipid profiles in patients with thalassemia major have been reported in diverse ranges in various studies (23–25). Different results of studies on lipid profiles in these patients are affected by the level of liver damage, reduced activity of intra- and extra-hepatic lipase enzymes, and the removal of LDL-C and HDL-C by monocytes and active macrophages and hormonal disorders (21–23). Princen et al. showed that green tea consumption of six cups a day (900 milliliters) had no significant effect on serum lipid profile and LDL oxidation (24). Furthermore, in a study by Miura et al., consuming 300 mg green tea extract twice a day for one week in 22 healthy volunteers did not significantly change serum lipid profiles (25). Epidemiological studies have shown that drinking 5 to 10 cups of green tea per day reduces plasma cholesterol levels (26–28). Animal studies have also confirmed the effect of green tea on serum cholesterol levels (29–31). Green tea inhibits intestinal cholesterol absorption and increases cholesterol excretion through feces, which is expressed as the main mechanism for reducing cholesterol (32). In vitro studies have shown that green tea extract increases the expression of LDL receptors and regulates the metabolism of cholesterol in HepG2 cells (3). Christina et al. found that the consumption of green tea extract for four weeks in rabbits that received high-fat diet reduced total serum cholesterol and C-LDL levels and improved serum lipid profile. Moreover, the extract of green tea reduced the activity of cholesterol synthesis and increased LDL receptor activity in the liver and increased fat excretion through feces (15). According to the mentioned mechanisms, the results of the present study confirm the beneficial effects of green tea on the reduction of blood cholesterol.

In patients with major β – thalassemia, liver enzymes (ALT and AST) increase when the liver is impaired. Liver enzymes (ALT) are the indicators of liver injury and their increase in patients with thalassemia is indicative of impaired liver function (34). According to the results of this study, the baseline levels of liver enzymes were high in both groups relative to the normal value (<40 U/L), but close to the normal range, indicating a relatively favorable status of liver function in the subjects. Green tea consumption for eight weeks in these patients did not significantly change the liver enzymes among the study groups. However, intra-group

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changes showed a significant reduction in the levels of liver enzymes after the intervention, which was higher in the green tea group than in the control group. Various studies also have shown increased liver enzymes in patients with thalassemia major. This increase has been attributed to hepatocellular damage in these patients (35, 19). Regarding the effects of green tea on liver enzymes in patients with thalassemia, no study has been conducted so far. Several animal studies have investigated the role of green tea in improving the damage and liver disorders. Green tea protects CYP21 from oxidative stress and reduces iron toxicity in hepatocytes (Hep G2) (36). In other studies, it has been shown that green tea inhibits lipid peroxidation in the liver of rat through iron chelating by removing free radicals (22). Green tea catechins use their proteins to enter the liver cells and react with reactive oxygen species in the liver cells (11).

Similar to DFO and DFP, green tea with its iron chelating properties can eliminate ROS in the liver cells. Green tea, on the other hand, has no toxic effects on the liver because it has no side effects (8, 11). Green tea inhibits lipid peroxidation in the liver through iron chelation and the elimination of free radicals (37). Green tea catechins use their proteins to enter the liver cells and react with reactive oxygen species in the liver cells (11). In the present study, intra-group reduction in liver enzymes was also observed in the control group, but the reduction rate was lower than that of the green tea group. The observed decrease in the control group can be related to the effects of medications in these patients and the proper control of the disease.

According to the results of the present study, there was no significant difference in the intake of energy and macronutrients, weight and BMI at the beginning and the end of the study between the two groups. So far, no studies have been conducted on the effects of receiving green tea on nutritional intake and anthropometric indices in patients with major β–thalassemia or in those with iron overload. Studies on the supplementary effects of green tea extract and green tea drink have reported varied results regrading anthropometric indices in different diseases. In a study by Fukino et al., after receiving green tea supplement (containing 456 mg of catechins) for four months, there was no significant change in the intake of calories, carbohydrates, protein and fat. Moreover, the green tea supplement did not significantly change the weight of subjects during the study (38). In the study of Nagao et al., after receiving green tea (340 ml) for 12 weeks in 240 healthy volunteers, there was no significant change in the intake of energy in the studied groups (39).

Furthermore, in the study of Taghyan et al., green tea consumption did not significantly affect weight, BMI, and food intake (40). In another study by Chan et al., the use of green tea extract for three months in obese women with polycystic ovary syndrome also had no significant effect on body weight and BMI (41). In the study of Kajimoto et al., daily consumption of green tea containing 646 mg of catechin for three months reduced the weight by 0.4 kg (42). In another study, the effect of daily 750 mg green tea extract in three capsules containing 250 mg for three months reduced the weight by 0.7 kg in obese subjects (43).

In a study by Babu et al., 300 mg/kg of green tea extract in diabetic rats for four weeks led to weight gain in rats. In this study, the cause of weight gain was attributed to the improvement of glycemic status compared to the control group (44).

In the present study, green tea consumption did not significantly change the dietary intake and anthropometric indices at the end of the study. In this way, the above variables were not considered as confounding factors in interpreting the biochemical outcomes previously mentioned. Limitations of the study: In this study, there was not the possibility to prepare a placebo for green tea. The results of this study showed the beneficial effects of green tea consumption on the reduction of levels of liver enzymes, triglycerides and especially total serum cholesterol in patients with thalassemia major.

Acknowledgment

Hereby, we would like to thank the Research Deputy of Tabriz University of Medical Sciences for the financial support of this project, as well as all the participants and colleagues in Shahid Ghazi Tabatabai Hospital in Tabriz who were involved in this research.

[DOR: 20.1001.1.15614107.1397.20.8.2.4]
[DOI: 10.18869/acadpub.jbums.20.8.15]

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