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ΠΡΩΤΟΤΥΠΗ ΕΡΓΑΣΙΑ

Full resting echocardiographic study of left ventricle in children with b-thalassemia major

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Abstract Our objective was to investigate the cardiac status of patients with b-thalassemia major who received regular transfusions and chelation therapy, to assess the incidence of subclinical abnormalities of the myocardium and to study the relationship between the above possible disorders and age, serum hemoglobin and ferritin levels, duration and compliance to chelation therapy. Ninety three b-thalassemia major patients aged 2.5 to 18 years old and forty-three age and sex matched controls (3-17 years od) were studied. The cardiac evaluation included a clinical examination, x-ray films of the chest, electrocardiography and echocardiography. The cardiothoracic ratio was increased in 7/93 patients (8%) and electrocardiographic abnormalities were present in 11/93 patients (12%). Echocardiographic abnormalities were observed in 8/93 patients (9%) and three of them suffered from dilated cardiomyopathy. B-thalassemia patients had also increased mean left ventricular end-diastolic diamension (LVDd), left ventricular mass and mass index compared to controls, while mean ejection fraction and fractional shortening were decreased. In Doppler echocardiographic measurements there was an increased mean rate of deceleration of flow velocity (EF slope), increased mean ratio between early and late peaks of flow velocity (E/A) and decreased mean deceleration time (dt). 1) The majority of patients with b-thalassemia major who receive regular transfusions and chelation therapy, have no serious cardiac involvement until the age of eighteen years old. 2) The earliest signs of dilated cardiomyophathy in echocardiography are the increased LVDd and mass index and in Doppler echocardiography the increased EF slope, the increased E/A and the decreased dt. 3) Patients with higher serum ferritin levels had higher mean LVDd, while mean ejection fraction and fraction of shortening were lower. 4) The compliant patients to chelation therapy had a lower incidence of overt cardiac disease than non-compliant patients.
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INTRODUCTION

The introduction of highly controlled regimen of blood transfusions and chelation therapy has substantially improved the survival rate of beta-thalassemia major patients, as it delays the appearance of hemosiderosis effects in the myocardium. Nevertheless, cardiac involvement remains the most frequent cause of death among these patients (63%) and the early mortality rate remains elevated, even when patients are treated with desferrioxamine (DFO)[1,2].

Our objective was to investigate the cardiac status of patients with b-thalassemia major receiving regular transfusions and chelation therapy, to assess the incidence of subclinical abnormalities of the myocardium and to study the relationship between the above possible disorders and age, serum hemoglobin, serum ferritin levels, duration and compliance to chelation therapy.

SUBJECTS AND METHODS

In this progressive study ninety three patients, 51 boys and 42 girls, aged 2.5 to 18 years old (mean age 11.9 ± 4.6 years) affected by the homozygous form of b-thalassemia major, were studied. All patients were receiving regular blood transfusions in order to maintain their hemoglobin levels above 10 g/dl and they started chelation therapy with DFO in serum ferritin level up to 1000 ng/ml.

Compliance to chelation therapy, as well as the total number of blood transfusions, mean post-transfusional hemoglobin levels and mean serum ferritin levels were recorded in each patient's file. The mean hemoglobin level and the mean serum ferritin level derived from the corresponding mean values over the last 5 years. As for the compliance to chelation therapy, patients were characterized as compliant (chelation therapy 5-6 times a week), moderately compliant (chelation therapy 4-5 times a week) and non-compliant (chelation therapy less than three times a week).

Forty-three normal individuals (21 boys and 22 girls), aged 3-17 years old (mean age 11.1±4.1 years) were selected as control subjects. They were healthy and they did not have anemia or any clinical, radiological, electrocardiographic or echocardiographic evidence of congenital or acquired heart disease.

Patients and control subjects underwent an evaluation that included a complete medical history, clinical examination, posteroanterior x-ray film of the chest, electrocardiography (ECG) and echocardiography. The height and weight of each patient and of each control subject was recorded and the body surface area was calculated.

Clinical examination and echocardiography were obtained in all patients within 48 hours after the blood transfusion, so that Doppler diastolic indices were not influenced by possible changes in ventricular loading[3]. The posteroanterior x-ray films were reviewed in order to calculate the cardiac to thoracic ratio. A ratio >55% in infants and young children and >50% in older children, was considered as cardiomegaly[4].

Left ventricular hypertrophy on the ECG was estimated according to Garson criteria in patients younger than 15 years old[5] and according to Romhilt & Estes criteria for patients older than 15 years old[6].

The echocardiographic study (M-mode, two-dimensional and Doppler) was obtained using 5 MHz captors in younger children and 3.5 MHz captors in older ones. M-mode measurements of the systolic function of left ventricle were obtained according to the recommendations of the American Society of Echocardiography[7]. The curves of the blood flow velocity through the mitral valve were recorded with a pulsed Doppler ultrasound from an apical four-chamber view, in order to estimate the diastolic function of the left ventricle. The sample volume was placed between the tips of the mitral leaflets, about 1 cm below the valve, at the point where the maximal flow velocity in early diastole was obtained[3,8]. The obtained echocardiographic measurements (M-Mode, 2D and Doppler) are summarized in Table 1.

Table 1. Echocardiographic measurements in patients with b-thalassemia major

M-mode measurements:
Left Ventricle Diameter Diastole (LVDd)
Left Ventricle Diameter Systole (LVDs)
Intraventricular Septum Diastolic diameter (IVSd)
Intraventricular Septum Systolic diameter (IVSs)
Left ventricular posterior wall thickness in diastole (LVPWd)
Fraction of Shortening (FS)
Left Atrial Cavity Diameter (LA)
Left Ventricle Mass (Mass)
Left Ventricle Mass Index (Mass Index)
2D measurements:
Left Ventricle Diastolic Volume (LVD Vol)
Left Ventricle Systolic Volume (LVS Vol)
Left Ventricular Ejection Fraction (EF)
Doppler measurements:
Peak mitral flow velocity in early diastole (E)
Peak flow velocity during atrial contraction (A)
Rate of deceleration of flow velocity in early diastole (EF slope)
Flow velocity deceleration time (dt)
Ratio between the early and late peaks of flow velocity (E/A ratio)

STATISTICAL ANALYSIS

Statistical analysis was performed using the SPSS for Windows 95 and StatCalc by Epilnfo 2000 programs. Results are presented as means±SD. The normal distribution goodness of fit of the quantitative variables was checked, using the Kolmogorov - Smirnov non-parametric test. For the biostatistical hypothesis tests, we applied either the parametric method of student t-test for independent samples, or the analysis of variance (ANOVA), depending on the nature of the comparison. Finally, multiple regression models were applied in order to define the independently related variants with ferritin levels[9]. A value of $p<0.05$ was considered statistically significant.

RESULTS

The mean value of body weight, height and body surface of b-thalassemia patients was lower than control subjects, without a significant statistical difference (Table 2).

The cardiothoracic ratio was increased in 7/93 patients (8%). Electrocardiographic abnormalities were present in eleven out of the 93 patients (12%), but only seven children out of these eleven, aged >15 years, had serious abnormalities in their ECG (left ventricular hypertrophy, ventricular premature beats, atrial flutter and fibrillation). A dilated cardiomyopathy (DC) was detected by ultrasound in three patients with cardiomegaly and severe electrocardiographical abnormalities.

Table 2. Variations of weight, height and body surface area in healthy subjects and b-thalassemia major patients

	Healthy		Patients		
Mean	SD	Mean	SD	p	
Body Weight (Kg)	43.31	16.68	39.32	14.45	NS
Body Height (cm)	145.6	23.12	144.75	20.08	NS
Body Surface (m^2)	1.31	0.36	1.25	0.32	NS

Ultrasound evaluation of left ventricle systolic function

An increased left ventricular end-diastolic diameter (LVDd) was established in six out of the 93 patients (6.5%), three of which were suffering from DC.

The mean values of LVDd, LVDs, IVSs, LV PWd and LA were increased in patients compared to controls, without a statistically significant difference (Table 3).

Ejection fraction (EF) and fraction of shortening (FS) ranged in normal values in all patients, except of two, who were suffering from DC and finally died. Their mean values, however, were lower among the patients compared to controls, with a significant statistical difference ($p<0.01$).

The mean value of left ventricular mass was higher in patients, with a non-significant statistical difference ($p=0.21$), while the mean value of left ventricle mass index (MI) was greater in patients, with a statistically significant difference ($p<0.05$) (Table 3). It was also noted that as the age increases, MI increases too with a statistically significant difference ($p<0.05$) in patients, while the difference is not statistically significant ($p=0.32$) in control subjects (Fig. 1).

Table 3. M-Mode, 2D and Doppler echocardiographic results in healthy subjects and b-thalassemia major patients.

	Healthy		Patients		
	Mean	SD	Mean	SD	p
LVDd	42.50	5.70	43.89	6.11	NS
LVDs	26.15	4.43	27.77	7.21	NS
IVSd	8.25	1.65	8.16	1.68	NS
IVSs	11.13	1.71	11.48	2.04	NS
LVPWd	7.67	1.36	8.28	1.73	<0.05
FS	37.90	3.40	35.59	4.74	<0.01
LA	28.07	3.99	28.68	3.98	NS
Mass	120.21	50.36	132.80	55.47	NS
Mass Index	90.85	20.18	102.74	29.05	<0.05
LVDVol	83.28	26.70	89.41	29.37	NS
LVSVol	26.58	9.73	31.84	15.08	<0.05
EF	68.26	4.18	65.04	6.61	<0.01
E	85.98	11.73	84.37	14.73	NS
A	37.81	7.12	36.76	9.31	NS
EF slope	806.64	130.36	831.34	169.22	NS
dt	107.67	13.06	103.04	16.49	<0.05
E/A ratio	2.33	0.45	2.40	0.57	NS

Other echocardiographic findings in b-thalassemia major patients were mitral valve prolapse in 8 patients, mild mitral valve insufficiency in 4 patients, mild to moderate tricuspid insufficiency in 4 patients and mild pulmonary insufficiency in 1 patient.

Ultrasound evaluation of left ventricle diastolic function

Three out of the 93 patients with b-thalassemia presented diastolic abnormalities. More specifically, abnormal relaxation pattern (↑A, ↓E/A,↑dt) was noted in one patient who suffered from DC. Left ventricular restrictive abnormalities (↓A, ↑E/A, ↓dt) were noted in the other two patients who suffered from DC and died.

The mean value of the rate of deceleration of flow velocity in early diastole (EF slope) and the ratio between the early and late peaks of flow velocity (E/A ratio) where higher in our patients, compared to control subjects, without a statistically significant difference. On the contrary, the mean value of the flow velocity decelaration time (dt) was lower in patients, with a significant statistical difference ($p<0.05$).

Consequently, eight out of 93 patients with b-thalassemia (9%), all aged 10 years and older, presented pathological indices in their echocardiographic study of left ventricle.

Other statistical comparisons

The patients with the highest hemoglobin levels before transfusion presented a lower cardiothoracic ratio (Fig. 2).

For the group of patients we observed increase of the M-mode echocardiographic parameters as the years of chelation therapy were increasing ($p<0.001$). As far as the ferritin levels there was a statistical significant correlation only with the left atrium diameter (LA) and LVDs ($p<0.05$), while the EF and FS were decreasing in a non significant statistical rate as the ferritin was increasing.

Furthermore there was a positive correlation between compliance of patients and EF and FS, but without a significant statistical difference. On the other hand as compliance increased LA, LVDd and LVDs decreased with a significant statistical difference ($p<0.05$).

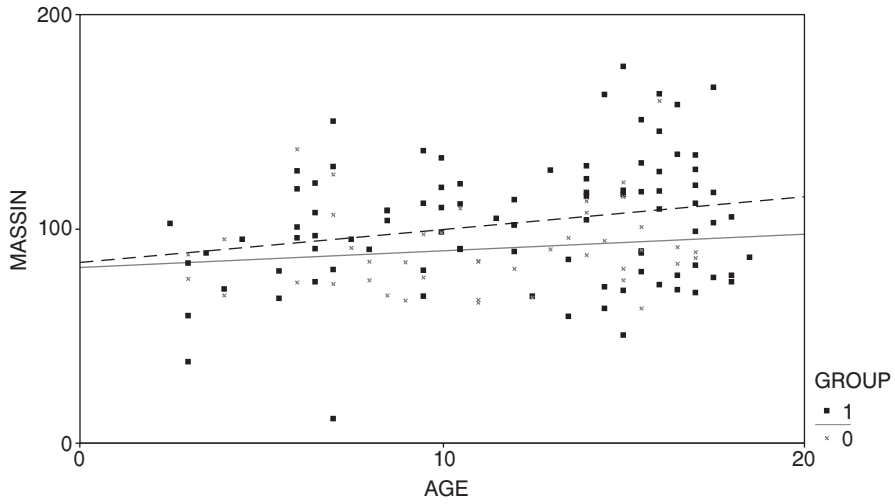

Fig. 1. Relationship between between the age and left ventricle mass index (MASSIN) in healthy subjects (Ψ) and b-thalassemia major patients (— -).

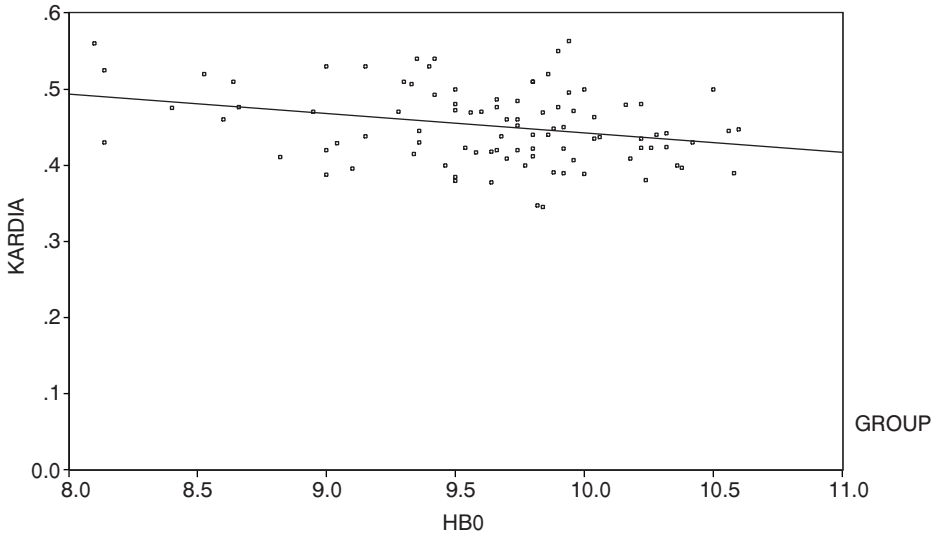

Fig. 2. Relationship between the cardiothoracic ratio (KARDIA) and post-transfusional hemoglobin (HBO) in b-thalassemia major patients.

DISCUSSION

Studies on the cardiological implication of patients with b-thalassemia that underwent chelation therapy since the beginning of their disease are few and relatively recent[10-13]. In these reports, it is noted that there is an increase of survival after the prompt implementation of chelation therapy.

An interesting finding before the extensive application of chelation therapy was the great frequency of cardiomegaly (cardiothoracic ratio 32% and 18%) and of pathological ECG (16% and 61%)[14,15]. Also, in studies where the reported patients started chelation therapy in different ages, the mean value of the body surface area was considerably lower, with a significant statistical difference[8,13,16].

In the present study the mean value of body surface area was lower in patients than in controls without a statistically significant difference. We also established cardiomegaly in only 8% of the patients, and a pathological ECG in 12%. In addition, the most serious echocardiographic abnormalities were noted in patients above 15 years old, as well as in the three patients with DC. The above results constitute serious evidence that there is a significant decrease of the pathological findings in patients receiving

regular transfusions and chelation therapy.

Six out of the 93 patients (6.5%) had increased LVDd. The mean value of EF and FS was lower in patients compared to controls, with a statistically significant difference ($p<0.01$). The lower value of FS in patients might be due to the increase of the LVDs. The mean value of MI was greater in patients than in controls with a statistically significant difference ($p<0.05$), which is possible due to the relatively smaller body surface that the b-thalassemia patients have.

In a previous echocardiographic study a dilated cardiomyopathy was established in 4 out of the 76 patients aged 4 to 38 years old and an increased LVDd in 8 out of the 76 patients. In this study there was a group of patients that did not start chelation therapy promptly[17].

Valdez-Cruz et al.[13] followed 13 patients, aged 2 to 15 years old , who started chelation therapy since the beginning of their disease and they observed that there was an increase of the LVDd and LVDs in patients, with a statistically non-significant difference compared to controls, as well as a decrease of the FS with a statistically significant difference ($p<0.05$).

Favilli et al compared 25 b-thalassemia major patients (mean age of 15.8 ± 5.7 years, with a regular regimen of blood transfusions and chelation therapy) to 25 healthy subjects. In this report the mean value of LVDd and left ventriclular MI was significantly increased in patients compared to controls ($p<0.001$ and $p<0.05$ respectively). The LVDd was also significantly increased even among the patients with normal systolic function, compared to controls[11]. The higher mean value of LVDd found in this study might be due to the greater age range of these patients.

Consequently, as far as the systolic function of the left ventricle is concerned, it is apparent in our study as well as in other previous studies, that despite regular chelation therapy there is still an increase of the LVDd as an early symptom of the incipient DC. Patients with b-thalassemia major also present an increased mean value of the cardiac MI, while the mean values of FS and EF are lower among patients than in control subjects, before the appearance of heart failure.

From the evaluation of the diastolic function of left ventricle, we noted an increase of EF slope and E/A ratio in our patients compared to controls, without a significant statistical difference. On the contrary, the mean value of dt was lower in patients, with a statistically significant difference ($p< 0.05$). This finding was attributed to the fact that the b-thalassemia patients have a smaller body surface area in comparison to the control group and it is in agreement with an earlier study in a Greek population[8].

There are few reports on the diastolic left ventricular function in the literature. Spirito et al[18] studied 32 b-thalassemia patients without cardiac disease. Twenty of them started chelation therapy at the age of 3 to 9 years old, 11 started older than 10 years, and one refused to undergo chelation therapy. They noted that 50% of the patients had pathological findings compared to the 32 healthy control subjects: b-thalassemia patients presented an increase of E wave ($p<0.01$), EF slope ($p< 0.001$), E/A ratio ($p<0.001$) and a decrease of dt ($p<0.001$). Kremastinos et al.[8] also studied 88 b-thalassemia patients who had started chelation therapy in various ages, and 46 healthy control subjects. In this report it was established that there was a significant increase of E wave, A wave, and EF slope, while the E/A ratio did not present a statistically significant difference. Left ventricular restrictive abnormalities (↑E/A and ↓dt) were established in 7/88 patients (8%) all aged 20 years and older and with elevated levels of serum ferritin. It is apparent from the above study that the true restrictive left ventricular filling abnormalities develop in the advanced stages of the disease and that the myocardial iron deposition has only a slight effect on the left ventricle diastolic function indices until the final stages of the disease.

In our study we had lower percentages of pathological indices of the left ventricle diastolic function, in comparison to earlier studies. Our findings were attributed to the younger ages of our patients and to the regular regimen of blood transfusions and chelation therapy. The earliest abnormality that the b-thalassemia patients present is the increase of the EF slope[18], a fact that was established in our study as well.

As far as ferritin levels is concerned, it was established in our study that the b-thalassemia patients with the worst compliance to chelation therapy had higher ferritin levels. Moreover, as the ferritin levels increased, all the M-mode echocardiographic indices increased too, while the EF and FS were lower among the patients compared to controls.

According to Aldouri et al.[19], high ferritin levels do not reflect the degree of cardiac hemosiderosis, because patients with similar iron loads differ in the degree of cardiac dysfunction. On the other hand, Lai et al.[20] showed that patients with mean serum ferritin levels <1000 ng/ml had lower incidence of complications (5% of them had cardiac disease), while in patients with mean serum ferritin levels >1000 ng/ml the overall risk of complications increased 10-fold (49% of them had cardiac disease). We did not find any other such studies in the literature.

In the multivariate analysis that was conducted in our study, it was found that only ferritin levels had a statistically significant difference to compliance to chelation therapy. It was also established that the group of patients with optimal compliance to chelation therapy had fewer electrocardiographic and echocardiographic abnormalities, compared to the less or non-compliant patients. Our last finding is in agreement with the findings of other authors[21-24].

CONCLUSIONS

In our study we were able to establish that the majority of the children suffering from the homozygous type of b-thalassemia receiving regular transfusions and chelation therapy, have a normal ECG and normal systolic and diastolic function of the left ventricle, up to the age of eighteen years old.

The earliest echocardiographic findings that were noted in the M-mode echocardiography included increased LVDd and cardiac mass index, while in Doppler echocardiography increased EF slope, increased E/A ratio and decreased dt were observed.

Patients with higher serum ferritin levels have higher mean LVDd, as well as higher mean values in other parameters in the M-mode echocardiography, while mean values of EF and FS are lower.

Finally, as far as the compliance to chelation therapy is concerned, compliant patients have a lower incidence of overt cardiac disease than non-compliant patients.

Based on this study it becomes apparent that regular regimen of blood transfusions and chelation therapy, combined with a good compliance, can lower cardiac complications and delay the development of cardiomyopathy.

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ΠΕΡΙΛΗΨΗ

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Σκοπός της μελέτης ήταν να ελεγχθεί η κατάσταση του μυοκαρδίου των πασχόντων από ομόζυγη β-Μεσογειακή αναιμία (β-ΜΑ) που βρίσκονταν σε τακτικό πρόγραμμα μετάγγισης-αποσιδήρωσης από την αρχή της νόσου, η ανίχνευση πρώιμων διαταραχών της καρδιακής λειτουργίας και η συσχέτιση των καρδιολογικών ευρημάτων με την ηλικία, τα επίπεδα της αιμοσφαιρίνης και φερριτίνης του ορού, τη διάρκεια αποσιδήρωσης και το βαθμό συμμόρφωσης σε αυτήν. Μελετήθηκαν 93 πάσχοντες από ομόζυγη β-ΜΑ ηλικίας 2,5-18 χρόνων και 43 υγιή παιδιά ηλικίας 3-17 χρόνων. Ο καρδιολογικός έλεγχος περιλάμβανε κλινική εξέταση, τηλεακτινογραφία καρδιάς, ηλεκτροκαρδιογράφημα και ηχοκαρδιογράφημα. Ο καρδιοθωρακικός δείκτης βρέθηκε αυξημένος σε 7/93 πάσχοντες (8%) και παθολογικά ευρήματα στο ΗΚΓ σε 11/93 (12%). Παθολογικές τιμές στη μελέτη της αριστερής κοιλίας είχαν 8/93 ασθενείς (9%), τρεις από τους οποίους έπασχαν από διατατική μυοκαρδιοπάθεια. Οι πάσχοντες από β-Μεσογειακή αναιμία εμφάνιζαν αύξηση της μέσης τιμής της τελοδιαστολικής διαμέτρου της αριστερής κοιλίας (LVDd), της μάζας της αριστερής κοιλίας και του δείκτη μάζας, ενώ η μέση τιμή του κλάσματος εξώθησης και κλάσματος βράχυνσης ήταν ελαττωμένη. Στο Doppler παρατηρήθηκε αύξηση της μέσης τιμής της EF κλίσης και της σχέσης E/A, καθώς επίσης ελάττωση της μέσης τιμής του χρόνου επιβράδυνσης (dt). 1)Οι περισσότεροι ασθενείς που βρίσκονται σε τακτικό πρόγραμμα μετάγγισης-αποσιδήρωσης από την αρχή της νόσου έχουν στο μεγαλύτερο ποσοστό φυσιολογική καρδιακή λειτουργία μέχρι την ηλικία των 18 χρόνων. 2) Τα πιο πρώιμα ευρήματα ενδεικτικά της αρχόμενης διατατικής μυοκαρδιοπάθειας είναι η αύξηση της LVDd και του δείκτη καρδιακής μάζας, ενώ στο Doppler η αύξηση της EF κλίσης και της σχέσης E/A, καθώς επίσης η ελάττωση του dt. 3) Οι ασθενείς που έχουν υψηλότερες τιμές φερριτίνης, έχουν μεγαλύτερη μέση τιμή LVDd στο M-Mode ηχοκαρδιογράφημα, ενώ η μέση τιμή του κλάσματος εξώθησης και κλάσματος βράχυνσης είναι χαμηλότερες. 4) Οι καλύτερα συμμορφούμενοι ασθενείς έχουν καλύτερη καρδιακή λειτουργία από τους μη συμμορφούμενους.

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