Influences of Thyroid Hormones on the Alteration of Autonomic Nervous System in Female Patients with Overt Hyperthyroidism

CRISTINA TUDORAN, AHMED ABU AWWAD*, CATALINA ONCU GIURGI, TUDOR CIOCARLIE, MARIA RADA, MARIANA TUDORAN
University of Medicine and Pharmacy Victor Babes, 2 Eftimie Murgu Sq.,300041, Timisoara, Romania

The aim of this study is to document the impact of thyroid hormones on the autonomic nervous system (ANS), expressed by heart rate variability (HRV) and heart rate turbulence (HRT), in patients with hyperthyroidism, compared to controls. Another purpose is to determine if HRV and HRT parameters are significantly correlated with the levels of thyroid hormones and the duration of hyperthyroidism. We studied HRV, in time and frequency domain, and HRT in a group of 113 premenopausal women, with still untreated overt hyperthyroidism, without cardiovascular diseases or risk factors for atherosclerosis, admitted between 2015 and 2018 in the Endocrinology Clinic of our hospital and compared the results with data obtained in 29 healthy controls. Depending on the severity and duration of hyperthyroidism and levels of thyroid hormones, patients were assigned to three groups: mild and moderate hyperthyroidism, severe and recurrent forms. We performed 24 hours Holter monitoring in patients and controls. Regarding HRV parameters in time domain, they were significantly depressed in patients comparing to controls. Referring to HRT, all patients had abnormal, positive values of turbulence onset (TO) and we documented statistically significant differences ($p<0.001$) when compared to controls. All patients had normal positive values of turbulence slope (TS), which decreased parallel with the severity of hyperthyroidism. In patients with hyperthyroidism, we documented depressed values of HRV parameters in time domain, correlated with the duration and severity of the thyroid disease. Our patients had pathologic values of TO. Although positive, TS values were lower when compared to controls.

Keywords: hyperthyroidism, free thyroxine, triiodothyronine, heart rate variability, heart rate turbulence, norepinephrine

Hyperthyroidism determines a hyperkinetic state suggesting an imbalance of the autonomic nervous system (ANS) [1]. These alterations of the ANS balance can be documented by modifications of heart rate variability (HRV) and heart rate turbulence (HRT), aspects debated in several studies [2-4]. HRV describes the spontaneous fluctuations in heart rate (HR) and normal RR intervals and is widely used to characterize the status of the autonomic nervous system (ANS) [1-3]. Its analysis is used in both, physiological models, and in various pathological states for the assessment of cardiovascular risk. HRT studies the sinus rhythm cycle length variation after isolated premature ventricular contractions (PVC). These methods are used in studies to estimate the presence of sympathovagal imbalance in patients with congestive heart failure [2], or after myocardial infarction [5], in order to predict an increased cardiovascular risk and morbidity [5]. Some studies have evidenced that an increased HR, induced by sympathetic hyperactivity, is a negative prognostic factor [5]. The sympatovagal imbalance favours the onset of arrhythmias and increases the risk of sudden death [2,5-7]. The significance of these methods for the assessment of the cardiovascular risk in hyperthyroid patients, without other structural heart diseases, except the ones induced by thyroid hormones in excess, is still a subject to debate [8,9].

The objective of this study is to document the presence of HRV and HRT alterations in female patients with hyperthyroidism of various severity and duration and to evidence if there are statistically significant correlations between their parameters and the levels of thyroid stimulating hormone (TSH), free thyroxin (FT_4) and/or the duration of the disease.

Experimental part

Thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3) exert on the heart and vessels several genomic and nongenomic mediated effects. T_4 is the principal form, acting as a prohormone. Most of T_4 is converted to biologically active T_3 through the removal of an iodide by type 1 deiodinase [10]. One of their most obvious effects is a hyperkinetic state, similar to that induced by catecholamines in excess [1,9]. Because in patients with hyperthyroidism, normal or even lower levels of epinephrine and norepinephrine have been determined in serum and urine, it was assumed that the myocardium presents an increased sensitivity to catecholamines, possibly associated with an increased β-receptor density. The turnover of catecholamines is reduced in these patients. Thyroid hormones in excess alter the binding of catecholamines to receptors, as well as their affinity for specific receptors. In addition, in the heart, thyroid hormones increase the automatism and the intrinsic activity of the sinus node and reduce the vagal tone [11-13].

ANS represents an important part in the control of different physiological systems, (heart, brain, endocrine system). The main function of ANS is homeostasis, largely regulated by autonomic reflexes. The ANS has specific transmitter substances - mostly acetylcholine, epinephrine and norepinephrine - corresponding receptors and can be divided into preganglionic and postganglionic fibres. There are multiple interactions between ANS and endocrine system, for example: adrenal glands, thyroid hormones and even sexual hormones [13,14].

*email: ahm.abuawwad@gmail.com, Phone: +40745384087

Study group

From over 400 patients with overt hyperthyroidism, admitted in the Endocrinology Clinic of our hospital, over a period of three years (2015-2018), we selected 113 female patients. All of them were premenopausal, aged between 26 and 55 years (mean age 47.53 + 11.3 years) and still untreated with antithyroid drugs. Depending on the severity and duration of hyperthyroidism and the levels of thyroid hormones, patients were assigned to three groups: 46 patients with mild and moderate forms, 38 with severe hyperthyroidism with thyrotoxicosis and 29 recurrent cases, with repeated episodes of thyrotoxicosis. We ruled out all patients with subclinical hyperthyroidism. To prevent the influence of gender, hormonal status, associated pathology or risk factors on HRV and HRT, we excluded from our study group male patients and all postmenopausal women, the ones with diabetes mellitus, neurologic and respiratory pathology or other significant cardiovascular diseases, not related to thyrotoxicosis and also, those with systolic blood pressure values of over 150 mmHg and/or with diastolic of over 90 mmHg. In order to avoid the influence of drugs on HRV and HRT, we have not included in our study patients already treated with high doses of beta-blocker (low doses: 2.5 mg/day bisoprolol or nebivolol and 25 mg twice daily of Metoprolol were permitted). We excluded from the HRT analyse, subjects who were not in sinus rhythm or those with less than 5 isolated PVC on the 24 h Holter ECG recording. The results were compared with those obtained in a control group of 29 healthy women.

Methods

Thyroid evaluation

The diagnosis of hyperthyroidism was based on clinical picture and confirmed by the supressed levels of TSH and increased levels of free thyroxine (FT_4) and/or free triiodothyronine (FT_3). Serum TSH, FT_4 and FT_3 were measured by chemiluminescent microparticle immunoassay (CMIA), with the following normal values: TSH 0.465-4.67 mIU/L, FT_4 0.71-1.85 ng/mL (9.13-23.81 pmol/L), and FT_3 1.71–3.71 ng/mL (2.65-5.69 pmol/L). Thyroid ultrasonography (2D mode and colour Doppler) was performed using Siemens ultrasound system, with a linear transducer (5.0-14 MHz). In patients with suppressed TSH associated with thyroid nodule(s), the diagnosis of toxic adenoma, respectively toxic multinodular goitre was confirmed by 99mTc thyroid scintigraphy.

Cardiological evaluation: all patients and controls had 24 hours Holter monitoring performed with a Holter Labtech Cardiospy device. For the analysis of obtained data we used the Nevrokard Long-Term aHLV (L-aHRV V.5.0.0.) program. Regarding HRV, we studied the following parameters in time domain (TD): the standard deviation of all normal to normal (NN) intervals (SDNN), the standard deviation of all NN intervals occurred in 5 minutes (SDANN), the radical of the differences of mean squared NN successive intervals (RMSSD) and the HRV index (HRVTI); in frequency domain (FD): total power (TP), low frequency (LF), high frequency (HF) and LF/HF ratio. For HRT we determined the turbulence onset (TO) - early sinus acceleration after a PVC and the turbulence slope (TS) - late sinus deceleration following a PVC, according to guidelines [7].

Data analysis was performed using SPSSv.25.0 (Statistical Package for the Social Sciences, Chicago, IL, USA). Continuous variables were presented as a mean and standard deviation (SD) or median and associated quartiles (Q1, Q3) and categorical data were presented as counts (percentages). We performed descriptive and inferential statistics analysis to summarize the characteristics of the study population. To evaluate the proportion of HRV and HRT altered parameters in groups, we applied the chi-squared test ($\chi 2$). The results of the Shapiro-Wilk normality test showed a non-Gaussian distribution, which is why we continued to use nonparametric tests. For comparing patient groups, we used the Kruskal-Wallis H test, followed by a post-hoc analysis with Mann-Whitney U test with Bonferroni correction applied. In order to highlight the factors influencing HRV and HRT parameters, we analysed the strength of a linear relationship between them and the severity and duration of hyperthyroidism by using the Spearman's rank-order correlation. A p value of less than 0.05 was considered to indicate a statistically significance. The study was approved by the Ethics Committee of our hospital and all patients signed a written consent.

Results and discussions

In this study we analysed the fluctuation of HRV and HRT parameters in 113 female patients with overt hyperthyroidism of various severities, in comparison to controls. They had hyperthyroidism of various aetiology, mostly Graves disease (101 subjects - 89.38%) and toxic adenoma (12 patients - 10.61%). We selected only premenopausal women in our study because hyperthyroidism is ten times more frequent in women and sexual hormones also play an important role in the regulation of ANS, oestrogen increasing the parasympathetic parameters and progesterone the sympathetic ones of HRV.

Our aim was to document the alterations of HRV and HRT parameters in patients with hyperthyroidism, as well as the correlations between them and the severity and duration of thyroid disease. The results determined in hyperthyroid patients, as well as in controls, are presented in Table 1. There were no statistically significant differences concerning age and body mass index (BMI) ($p = 0.48$ and $p = 0.44$) between patients and controls.

Referring to HRV analysis in time domain, all parameters (SDNN, SDANN, RMSSD and HRVTI) were significantly depressed when compared to controls ($p<0.001$), (fig. 1). We observed that SDNN values were highly depressed in patients with severe hyperthyroidism (newly diagnosed and recurrent forms) and moderately reduced in those with mild/moderate forms, (table 1, fig. 1). Referring to HRV parameters in frequency domain, the statistical differences between patients and controls were not so conclusive. TP was reduced in patients with severe hyperthyroidism, compared to controls, but not in those with mild and moderate forms. LF and HF were higher in patients, but the LF/HF ratio was between normal limits, both in patients and controls, (table 1). Assuming that there could be statistically correlations between HRV parameters and the levels of TSH and FT_4 or the duration of the thyroid disease, we analysed our data with Spearman's correlation. Referring to SDNN, we documented a statistically significant positive correlation with TSH values ($r = 0.65$, $p<0.001$) and negative ones with FT_4 levels ($r = - 0.73$, $p<0.001$) and the duration of the disease ($r = - 0.4$, $p=0.002$). Regarding HRVTI, the correlation with TSH levels was positive and significant ($r = 0.83$, $p<0.001$) and negative and significant with FT_4 values and the duration of the disease ($r = - 0.7$, $p<0.001$, respectively $r= -0.39$, $p=0.003$).

Our results regarding HRV analysis in time domain, in patients with hyperthyroidism, are similar to those reported by other authors [9, 10, 15, 16] who also documented depressed levels of SDNN, SDANN, RMSSD and HRVTI in

these patients. We evidenced in all patients, statistically significant depressions of these parameters, comparing to controls, correlated with the severity and duration of hyperthyroidism. The results of HRV analysis, performed in frequency domain were less conclusive, only TP was reduced in patients with severe hyperthyroidism.

On the analysis of HRT parameters, all patients had abnormal, positive values of TO, with a statistically significant difference ($p<0.001$) when compared to controls, (fig.1). TS values, although normal, both in controls and in patients, were significantly lower in the last category, figure 1. Considering the existence of correlation between TO and thyroid hormones, we documented significant positive ones with FT_4 values and with the duration of the disease ($r= 0.68$, $p<0.001$, respectively $r=0.32$, $p=0.01$) and a negative, but significant one with TSH levels ($r = -0.72$, $p<0.001$). Referring to the correlation between TS and TSH it was positive and significant ($r =0.71$, $p<0.001$), with FT_4, it was negative and significant ($r = -0.27$, $p= 0.02$) and with the duration of hyperthyroidism it was negative, but not significant ($r = -0.2$, $p = 0.14$). Similar findings were presented in other studies [9,10,17].

The study of HRV and HRT is a highly debated topic in the literature and is used to ascertain the influences of the ANS on the heart [1,3,18]. Several scientific papers have been written about their significance in various physiological states and in pathological conditions [2,5,12]. Fluctuations of HRV and HRT parameters were observed in thyroid disorders [9,14,17]. Some authors, have studied their evolution in hypothyroidism [14,17] and others in hyperthyroidism [19,20] and have evidenced, on the short and long term Holter monitoring, a sympatovagal imbalance in treated and untreated patients [9, 19]. It is still debated if these alterations disappear after achieving the euthyroid state [9,14].

The hyperkinetic state encountered in hyperthyroidism, characterized by a sympathovagal imbalance, is similar to that induced by an excess of catecholamines [10, 11]. Kabir et al documented in their study [10] that all HRV parameters, measured in time and frequency domain, decreased progressively from euthyroid subjects to patients with subclinical hyperthyroidism ($p <0.001$). These data highlight the reduction of the vagal tone and the increase

Table 1

CHARACTERISTICS AND RESULTS OF HRV AND HRT ANALYSIS IN STUDY GROUPS

Clinical and laboratory characteristics and results of 24 hours Holter ECG monitoring in patients and controls	New cases with hyperthyroidism		Recurrent hyperthyroidism 29 patients	Controls 29 patients
	Mild and moderate forms 46 patients	Severe hyperthyroidism 38 patients		
Age, years	38.91 ±6.28	38.41 ±9.46	44.93 ± 6.22	42.94 ± 8.06
BMI, kg/m²	26.25 ± 1.12	25.76 ± 0.97	26.17 ± 1.23	26.28 ± 1.19
TSH, 0.46 – 4.68 μUI/mL	0.028 ± 0.03	0.009 ± 0.01	0.012 ± 0.02	2.64 ± 0.65
FT_4, 10-28.2 pmol/L	32.36 ± 8.3	51.61 ± 12.63	45.96 ± 18.55	15.08 ± 1.3
FT_3, 4.28-8.1 pmol/L	18.3 + 6.64	28.14 ± 4.6	26.94 ± 3.39	5.74 ± 0.74
Time since onset, months	6.6 ± 1.23	3.94 ± 0.89	34.26 ± 5.6	NA
HR, b/min	73.52 ± 4.9	75.05 ± 3.79	70.86 ± 5.61	63.52 ± 5.62
HRV				
• **Time domain:** SDNN, ms	90.3 ± 30.55	17.85 ± 1.88	15.99 ± 0.66	128.88 ±7.623
SDANN, ms	75.46 ± 35.21	6.91 ± 0.84	6.48 ± 0.71	134.47± 6.21
RMSSD, ms	17.89 ± 11.27	6.58 ± 0.99	6.72 ± 0.62	28.05 ± 5.19
HRVTI, ms	18.77 ± 5.11	6.12 ± 1.09	5.79 + 0.57	41.52 ± 10.89
• **Frequency domain:**				
Total power –TP, ms²	4183.8 ± 5332.3	2692.02 ± 556.2	2358.46 ± 2252.6	3078.7 ± 733.7
Low frequency - LF, ms²	1051.66 ± 518.7	1906.82 ± 572.8	1648.5 ± 1161.3	761.58 ± 115.4
High frequency- HF, ms²	379.77 ±143.3	785.14 ± 219.74	960.34 ±622.29	293.35 ± 67.24
LF/HF ratio	2.7 ± 0.64	2.62 ± 0.77	1.74 ± 0.45	2.71 ± 0.66
HRT: TO, %	1.71 ± 2,9	6.58 ±1.4	6.64 ± 0.78	-2.9 ± 0.65
TS, ms/RR	7.85 ± 1.11	4.95 ± 1.25	6.2 ± 0.57	10.65 ± 1.28

Legend: heart rate variability –HRV; heart rate turbulence – HRT; electrocardiogram – ECG; body mass index – BMI; thyroid stimulating hormone –TSH; free thyroxine - FT_4; free triiodothyronine - FT_3; heart rate –HR; standard deviation of all normal to normal (NN) intervals – SDNN; standard deviation of all NN intervals occurred in 5 minutes - SDANN, the radical of the differences of mean squared NN successive intervals – RMSSD; HRV index - HRVTI; turbulence onset – TO; turbulence slope – TS.

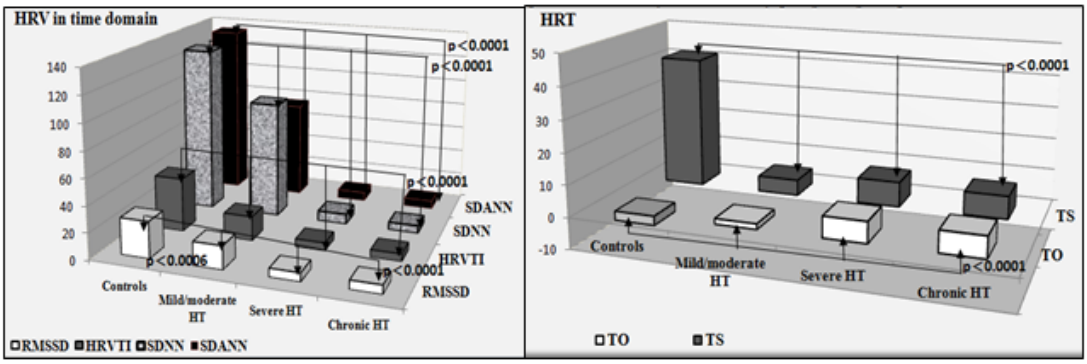

Fig. 1. HRV and HRT in study groups comparing to controls

Legend: heart rate variability –HRV; heart ate turbulence -HRT; standard deviation of all normal to normal (NN) intervals – SDNN; standard deviation of all NN intervals occurred in 5 minutes - SDANN, the radical of the differences of mean squared NN successive intervals-RMSSD; HRV index - HRVTI; turbulence onset – TO; turbulence slope - TS.

of the sympathetic cardiac control in hyperthyroidism, with important clinical implication taking into account that decreased HRV signifies an increased risk for arrhythmias. Other studies have reported a decreased parasympathetic cardiac activity in hyperthyroidism [11], effect that can be attributed to the interference between peripheral neuroeffector mechanisms and central inhibitory effects on cardiac baroreflexes. Chen JL [19] and Kabir [10] described in their studies an increased sympathetic activity in patients with hyperthyroidism.

HRT depression is considered an independent risk factor for the apparition of severe arrhythmias in patients after acute myocardial infarction and in those with heart failure [3]. Comparing to them, patients with hyperthyroidism, although presenting a sympatovagal imbalance, are prone to a lesser extent to ventricular arrhythmias, but mostly to supraventricular ones, especially to atrial fibrillation, aspect debated by some authors [21] in their articles [22,23].

Conclusions

In our study we have documented in patients with hyperthyroidism depressed values of HRV parameters in time domain, which were correlated with the duration and severity of the thyroid disease, expressed by FT_4 and TSH levels. We evidenced in our study group pathological values of TO, also correlated with the severity and the duration of hyperthyroidism. Although positive, TS values were lower comparing to controls.

References

1. MERZ C.N.B., ELBOUDWAREI O., MEHTA P., The Autonomic Nervous System and Cardiovascular Health and Disease. A Complex Balancing Act, JACC 2015; 3:383-5.

2. FLOREA V.G., COHN J.N., The Autonomic Nervous System and Heart Failure. Circulation Research, 2014; 23:1815-1825.

3. GERNOT E., Heart-Rate Variability-More than Heart Beats? Front Public Health. 2017; 5: 240. Published online 2017, Sep 11. doi: 10.3389/fpubh.2017.00240 PMCID: PMC560097, PMID: 28955705.

4. BAUER A., MALIK M., SCHMIDT G., BARTHEL P., CYGANKIEWICZ I., GUZIK P., Heart Rate Turbulence: Standards of Measurement, Physiological Interpretation, and Clinical Use. Journal of the American College of Cardiology, 2008; 52:1353-65.

5. COMPOSTELLA L., LAKUSIC N., COMPOSTELLA C., TRUONG L.V.S., ILICETO S., BELLOTTO F., Does heart rate variability correlate with long-term prognosis in myocardial infarction patients treated by early revascularization? World J Cardiol 2017; 9(1): 27-38.

6. TUDORAN, M., TUDORAN, C., CIOCARLIE, T., POP, G.N., BERCEANU-VADUVA, M.M., VELIMIROVICI, D.E., ABU AWWAD, A., BERCEANU-VADUVA, D.M., Mat.Plast.,**56**, no.1,2019, p.37-40.

7. SASSI R., CERUTTI S., LOMBARDI F., MALIK M., HUIKURI H.V., PENG C.K., SCHMIDT G., YAMAMOTO Y., Advances in heart rate variability signal analysis: joint position statement by the e-Cardiology ESC Working Group and the European Heart Rhythm Association co-endorsed by the Asia Pacific Heart Rhythm Society Europace 2015; 17:1341–1353.

8. KAMINSKI G., MAKOVSKI K., MICHALKIEWICZ D., KOWAL J., RUCHALA M., SZCZEPANEK E., The Influence of Subclinical Hyperthyroidism on Blood Pressure, Heart Rate Variability, and Prevalence of Arrhythmias, Thyroid 2012; 22:454-460.

9. OSMAN F., FRANKLYN J.A., DAYKIN J., CHOWDHARY S., HOLDER R.L., SHEPPARD M.C., Heart rate variability and turbulence in hyperthyroidism before, during, and after treatment. The American Journal of Cardiology 2004; 94:465–469.

10. KABIR R., BEGUM N., FERDOUSI S., BEGUM S., ALI T., Relationship of Thyroid Hormones with Heart Rate Variability. J Bangladesh Soc Physiol 2010; 5:20-26.

11. CHEN J.L., CHIU H.W., TSENG Y.J., CHU W.C., Hyperthyroidism is characterized by both increased sympathetic and decreased vagal modulation of heart rate: evidence from spectral analysis of heart rate variability. Clinical Endocrinology 2006; 64:611-616.

12. TUDORAN M., TUDORAN C., Kardiologia Polska, 73, No 5, 2015, 337.

13. TUDORAN, M., TUDORAN, C., VLAD, M., BALAS, M., ABU AWWAD, A., POP, G.N., Rev.Chim.(Bucharest),**70**, no.4, 2019, p.1372.

14. CELIK A., AYTAN P., DURSUN H., KOC F., OZBEK K., SAGCAN M., Heart rate variability and heart rate turbulence in hypothyroidism before and after treatment. Ann Noninvasive Electrocardiol 2011; 16:344-50.

15. GALETTA F., FRANZONI F., FALLAHI P., TOCCHINI L., BRACCINI L., SANTORO G., Changes in heart rate variability and QT dispersion in patients with overt hypothyroidism. Eur J Endocrinol 2008; 15885-90.

16. ESCO M.R., FLATT A.A., Ultra-Short-Term Heart Rate Variability Indexes at Rest and Post-Exercise in Athletes: Evaluating the Agreement with Accepted Recommendations. Journal of Sports Science and Medicine 2014; 13:535–541.

17. YILDIZ C., YILDIZ A., TEKINER F., Heart Rate Turbulence Analysis in Subclinical Hypothroidism. Acta Cardiologica Sinica 2015; 31:444–448.

18.TUDORAN, M., GIURGI-ONCU, C., ANDOR, B., ABU AWWAD, A., POP, G.N., BERCEANU-VADUVA, D., TUDORAN, C., Impact of Therapy with Selective Serotonine-Reuptake Inhibitors on the Evolution of Subclinical Atherosclerosis in Patients with Depressive Disorder, Rev.Chim.(Bucharest),**70**, no.5,2019, p.1685-1688.

19. CHEN J.L., TSENG Y.J., CHIU H.W., HSIAO T.C., CHU W.C., Nonlinear analysis of heart rate dynamics in hyperthyroidism. Physiological Measurement 2007; 28:427-37.

20. TUDORAN, C., TUDORAN, M., PARV, F., POP, G.N., ABU AWWAD, A., VLAD, M., BALAS, M., Factors Influencing the Evolution of Pulmonary Hypertension in Patients with Hyperthyroidism Rev.Chim.(Bucharest),**70**, no. 4, 2019, p.1328-1332

21. BIELECKA-DABROWA A., MIKAILIDIS D.P., RYSZ J., BANACH M., The mechanisms of atrial fibrillation in hyperthyroidism. Thyroid Research 2009; 2:4.

22. ABU AWWAD, A., PREJBEANU, R., VERMESAN, D., DELEANU, B., IONITESCU, M., FLORESCU, S., Dose effect of local Bethamethasone injection in low back pain. Rev. Chim. (Bucharest), **69**, no 9, 2018, p. 2382

23. ABU AWWAD, A., PREJBEANU, R., VERMESAN, D., BRANEA, I., DELEANU, B., FLORESCU, S., VLAD-DALIBORCA, C., Blood Loss of Pedicle Subtraction Osteotomy for Sagittal Imbalance Spinal Deformity. Rev. Chim. (Bucharest), **69**, no. 12, 2018, p. 3680

Manuscript received 19.11.2018