CHARACTERISTIC SIGNS ABOUT THE CONGRUENCE OF PATHOGENETIC MECHANISMS IN GENERALIZED PERIODONTAL DISEASE AND ANOREXIA NERVOSA

Maryna ANTONENKO[1], Ludmila RESHETNYK[2] , Serhii PALAMARCHUK[3], Mariana PALAMARCHUK[3] , Natalia ZELINSKAYA[4], Dmitro MALYI[2]

[1]MD, PhD, Prof.,"Bogomolets" National Medical University, Kiev, Ukraine
[2]MD, Assistant professor, "Bogomolets" National Medical University, Kiev, Ukraine
[3]MD, PhD, Chernivtsi, Ukraine
[4]MD, PhD, Assoc. Prof., Institute of Postgraduate Education, Kiev, Ukraine
Corresponding author: Serhii Palamarchuk; e-mail: serhiydentist@gmail.com

Abstract

Introduction. Early diagnosis of the initial degree of generalized periodontitis (GP) is an effective mode of secondary prevention. This is due to the complexity of understanding the etio-pathogenetic mechanisms of the development generalized parodontal diseases (GPD) and to their high association with a number of diseases of the internal organs and systems with common points of contact between interdependence and mutual influence, particularly with anorexia nervosa (AN). Recently, the incidence of AN has increased significantly, causing serious state, social, psychological and medical problems. The purpose of the present research was to establish the configuration features of generalized periodontal diseases and their clinical manifestations in the form of the basic characteristics of anorexia nervosa. **Materials and methods.** Clinico-radiological, immunological, analytical and statistical methods were used. 75 patients with AN, aged 18-36 years (average age 26±3.8) - the main group (M) - and 60 patients with GPD without signs of AN of the same age - comparison group (C), which consisted of two subgroups (C_1), (C_2) with different forms of gingivitis and GP, respectively - were investigated. The control group consisted of 30 subjects similar as to age and sex, without clinical signs of periodontal disease as well as diseases of the internal organs. **Results and disscussion.** A high incidence of GPD - up to 100% - was diagnosed, including both independent parodontal soft tissue disease and all components of the parodontal complex, characteristic for all age groups and varying with patient age, duration of AN and its stages. Among the independent forms of gingivitis, the most common was chronic catarrhal marginal gingivitis (86.7±8.8%), with some cases of exacerbation against the background of the overwhelming absence of complaints with single manifestations of agrarian, and complex psychological alliance. For all patients with GP, a high degree of tissue sensitization to the bone antigen, characterized by significant changes in the bone component of the parodontal complex with AN, was recorded. GP was predominantly of the I-II degree, with chronic course prevailing over other forms of GPD (80±4.6%). No advantages and priorities of different segments of parodontal complex lesions in patients with AN were observed. **Conclusions.** A direct correlation and interdependence of generalized parodontal diseases in the form of basic characteristics of AN were established.

Keywords: *generalized parodontal diseases, generalized parodontitis, hypersensibilisation, anorexia nervosa, osteoporosis, marginal catarrhal gingivitis.*

1. INTRODUCTION

According to recent epidemiological studies, the prevalence of GP is 60-100%, with a persistent tendency of increased frequency in young and employable people with gender and population preferences [1,2]. This circumstance causes serious state, social, medical and scientific concerns. Despite an increased dental culture of the population, which has been trending lately and prompts an early treatment, the result of the treatment of generalized parodontal diseases (GPD) is often unsatisfactory. This is due to some extent to the complexity of understanding their etio-pathogenetic mechanisms of development, and to the high association of GPD with a number of diseases of the internal organs and systems with common points of contact between interdependence and mutual influence [3].

A great number of researchers point out the high probability of pathogenetic communication of GPD with endocrine pathology, systemic diseases of human connective tissue, infraction vitamin, protein and lipid metabolism, emphasizing the thesis of associativity, affiliation and even comorbidity of these diseases in patients with such basic pathology [4-6]. However, the literature provides only fragmentary scientific

articles that suggest a possible correlation between anorexia nervosa (AN) and GPD, offerring a specific approach to the characteristics of their treatment, which, in our opinion, is a major drawback [7-9]. Recently, the incidence of AN has increased significantly, posing serious state, social, psychological and medical problems. According to WHO, in the general population, the prevalence of AN ranges from 0.37 to 1.0 per 100,000 population, with a frequency of 0.9- 4.3% in women and 0.3% in men, and it tends to significantly increase [10]. A particularly high risk of death was found with critically low body weight and later onset [11-13].

Significant changes associated with AN occur in the neuro-endocrine system, including the hypothalamus - pituitary - amygdala - genital and thyroid gland axis [14,15]. These changes are accompanied by a decrease in estrogen production, leading to pre-menarcheal amenorrhea and potentiating cortisol levels, abnormal secretion of insulin-like growth factor-1 and decreased thyroid hormone metabolism [16,17]. Hypoestrogenia can be a trigger for the development of osteopenia and osteoporosis, which leads to a decrease in bone mineral density [18,19]. Emerging hypogonadism and secondary hyperparathyroidism, as a result of a disorganized eating behavior in AN, the low calcium intake, and vitamin D deficiency and hypercorticism, may also be some of the important components that predispose patients with AN to GPD [18,19].

Clinical, radiologic, as well as laboratory diagnostics of advanced degrees of GP do not raise problems, yet the diagnosis of GP in initial stages presents certain difficulties. Thus, the absence of clear markers for identifying the initial changes in the key moment of the debut of the pathological process in GP renders difficult the diagnostic and, consequently, the establishment of a fully suitable and adequate treatment. Under such circumstances, the initial degree of GP is accepted and identified with different forms of gingivitis. As a result, the current treatment is interrupted, first of all, the inflammation process in the parodontal tissues, in order to reduce the activity of osteoclasts without the inclusion of funds that normalize the metabolism of the bone tissue of the alveolar process. Standard indicative criteria for the condition of the alveolar process, for example, the level of calcium, copper, strontium in blood plasma, bone-specific alkaline phosphatase, cholesterol, triglycerides of blood serum, oxyproline plasma, bone mineral density are quite burdensome for patients and are nonspecific indicators under the impact of many components of the body, which makes their utilization difficult and complicates the interpretation of facts. In our opinion, determination of tissue sensitization to bone antigen may involve an adequate specific reaction that could help an early diagnosis of GP.

In this regard, **the purpose** of the present research was to establish the features of the configuration of generalized parodontal diseases and their clinical manifestations in the form of basic characteristics of anorexia nervosa.

2. MATERIALS AND METHODS

The study was carried out at the "Bogomolets" National Medical University, Institute of Postgraduate Education, Kiev, Ukraine. The research was carried out in compliance with the principles of bioethics and rights of patients established in the Helsinki Declaration (2000) and the Fundamentals of Ukrainian legislation on health care (1992).

The work is a fragment of the research project entitled "Scientific substantiation of early diagnosis of generalized periodontal diseases of chronic and acute course", registration No.0118U100471.

Clinical and radiological methods of parodontal assessment were used to verify the diagnosis (according to the systematics of parodontal diseases of M.F. Danilevsky, 1994), as well as the immunological tests (inhibition of migrating leukocytes) by M. George method as a first type screening reaction, along with statistical methods performed in SPSS STATISTICA 6.0 and MS Excel 2010 (license number K9366093I 2016). Statistical analysis of data included calculation of mean values, standard deviation, and mean error.

Evaluation of tissue sensitization to bone antigen was determined in the inhibition of leukocyte migration (RILM). In the RILM reaction, a water-salt extract of bone tissue of

group 0 (I) Rh (D) was used. The migration index was calculated with formula:

$$IM = \frac{\text{migration area with antigen}}{\text{migration area without antigen}}, \quad \textbf{(1)}$$

where IM, equal to 0.1-0.5, corresponded to a high degree of sensitization.

The reaction was performed 24 hours after blood collection. Due to its high specificity and informativeness, the use of RILM was included in the list of reactions recommended by WHO. Taking into account that the reaction was carried out outside the body (*in vitro*), conditions were created for multiple examination of the patient for establishing the diagnosis and the stages of treatment.

The subjects of our research, who gave their informed consent, were 75 patients with AN, aged 18-36 years (average age 26±3.8) - the main group (M), and 60 patients without AN of the same age - the comparison group (C). For a detailed analysis of the clinical manifestations of GPD, all patients in the main (M) and comparative (C) groups were divided into several subgroups, as follows: the M_1 subgroup - patients with various forms of gingivitis, and the M_2 subgroup, including patients with generalized parodontities (GP), associated with AN as the basic pathology. All patients with AN followed a treatment in the neuropsychiatric department of Kiev Clinical Hospital on railway transport №1 (head of Department – O.V. Moskalenko). All examined patients had a restrictive form of AN. None of them had a cleansing form of AN.

The comparative (C) group consisted of two subgroups (C_1), (C_2) with different forms of gingivitis and GP, respectively.

The control group consisted of 30 people similar as to age and sex, without clinical signs of parodontal disease. Diseases of internal organs and systems, including the osteoarticular apparatus, were excluded.

3. RESULTS AND DISCUSSION

The research, as a whole, established a high incidence of GPD in patients with AN, including both independent soft parodontal tissue diseases and diseases of the entire parodontal complex (Table 1).

Table 1. Basic design of generalized parodontal diseases in patients of the main and comparative groups

Group of patients	Independent forms of gingivitis (without detailing the form and course of disease), number of patients (%)	Generalized parodontities (without detailing the degree and course of disease), number of patients (%)
The main group	15 patients (20±4.6%)	60 patients (80±4.6%)
The comparative group	48 patients (80±5.2%)	12 patients (20±5.2%)

In the research, independent parodontal soft tissue diseases of various forms and course of gingivitis were diagnosed in 20±4.6% cases, while GP of different degrees and course was observed in 80±4.6% in the main group.

It should be noted that patients of the comparative group without manifestations of anorexia nervosa had a higher incidence of independent forms of gingivitis - 80±5.2%, while GP of different degrees and course was diagnosed less frequently, being observed in 20±5.2% of the cases.

Analysis of the data of patients from subgroup M_2 showes that catarrhal gingivitis prevailed among the independent diseases of the soft parodontal tissues, no other forms of gingivitis being diagnosed.

Most of the patients had catarrhal gingivitis (86.7±8.8% cases), with an exclusively chronic course, while exacerbation of the process was observed only in 13.8±8.8% cases.

Realization of a detailed anamnesis in the patients of the main group and identification of complaints were difficult, due to the lack of a psychological alliance, accompanied by their lack of willingness to participate in voluntary contact during the examination, mostly because people with AN are unreliable "informants". Only a further structured interview helped gather information to evaluate the anamnestic features and complaints.

On the contrary, examination of patients in the (C) group for collection of anamnesis data and complaints was not difficult, as such patients

were ready for dialogue and open to participate in a therapeutic alliance.

In our opinion, the absence of any connotative dental complaints in patients of the (M) group could be due to the full focus laid exclusively on the paradigm of their aspect, pathological concern about their own weight, figure and low level of all components of compliance. However, in 20±10.3% of cases there was a so-called symptom of aeration, manifested by complaints of the inability to chew food, by unbearable pain when trying to bite off a piece of fresh bread, «pathological tooth mobility» and a feeling of tooth loss that did not respond to clinical changes.

It should be noted that in most of the patients of the M_1 subgroup, chronic gingivitis was characterized by involvement in the pathological process of only the marginal part of the gums. In most cases (66.7±12.2%), with a background of stagnant hyperemic and dense gums, a marked narrow band of stagnant hyperemia was observed in the area of cervical teeth. In 20±10.3% cases, the areas of congestive gum hyperemia were replaced by zones with marked pallor and only 13.8±8.8% cases of chronic inflammation covered all components of the soft tissues of periodontium.

Typically, the patients in the M_1 subgroup had supragingival dental calculus, in 26.7±11.4% cases appearing as a whole layer. According to the radiological examination of these patients, extension of periodontal fissures was established throughout, while maintaining the cortical plate. Osteoporosis of the apex of the alveolar bone ridge and bone components of the parodontal complex was evidenced.

It can be assumed that enlargement of the periodontal cleft and osteoporosis was due, on one hand, to chronic inflammatory process in the soft tissues of the parodontum, and on the other – the existing osteoporosis could be a manifestation of systemic osteoporosis caused by a decrease in estrogen production, abnormal secretion of insulin secretory factor and decreased thyroid hormone metabolism, resulting in hypogonadism, and secondary hyperparathyroidism.

Patients of the C_1 subgroup, unlike those of the M_1 subgroup, were diagnosed with all forms of gingivitis, including catarrhal, atrophic, desquamative, ulcerative-necrotic and hypertrophic, accounting for 77.1±6.1%, 4.2±2.9%, 6.3±3.5%, 2.1±2.1%, 10.4±4.4% cases, respectively. It should be noted that, unlike the patients in the (M) group, in the (C) group, a high motivational component was observed, which indicated willingness to take part to a full treatment.

Finalizing the analysis of subjective and clinical manifestations of the lesions of parodontal soft tissues affiliated with AN, the patients of the (M) group were characterized by: no complaints; low degree of psychological alliance with the doctor; catarrhal gingivitis with a predominant lesion of the marginal gums with chronic course; extension of the periodontal cleft and osteoporosis of the bone component of the parodontal complex.

In 60 patients (80.0±4.6%) out of the 75 of the (M_2) subgroup, GP of the initial to the second degree, and a chronic course with predominant absence of complaints were diagnosed on the basis of clinical and radiological examinations (Table 2).

Table 2. Distribution of parodontal lesions in patients with anorexia nervosa

Group of patients	GP, initial-I degree, chronic course	GP, I-II degree, chronic course
The main group	12 patients (20±5.2%)	48 patients (80±5.2%)

It should be noted that among the examined patients of the M_2 subgroup, GP had a chronic course, and only 3.3±2.3% cases showed exacerbation of the process, as a result of the recently transmitted infection. Symptomatic catarrhal marginal gingivitis was observed in soft parodontal tissues. In our opinion, the mainly chronic course of GP in patients of M_2 subgroup could be caused by significant changes in the general immunological reactivity of the organism due to AN, which did not allow to trigger an active inflammatory response.

Radiological examination of patients of the M_2 subgroup, with primary –I degree GP, evidenced extension of the periodontal fissure and osteoporosis of the bone component of the parodontal complex, the horizontal type of resorption in all patients, as well as cortical plate dislocation in the segment of the primary degree, and 1/3 reduced in the segment of I degree. No

advantages and priorities of different segments of the parodontal complex in patients with AN were observed.

When determining the hypersensitivity of the delayed action to bone antigen, all patients in this group showed a high degree of tissue sensitization, a sign of the significant changes produced in the bone component of the parodontal complex. This could be a predictor and an indicative factor that simplifies the diagnosis of initial -I degree GP, when the radiographic picture is not clear (Table 3).

Table 3. Frequency of tissue sensitization to the bone antigen in patients with generalized parodontal diseases and in almost healthy people

Groups of patients	Diagnosis	Tissue allergy	
		Number of patients	Bone antigen (inhibition of migrating leukocytes*)
Main group	GP, initial -I degree, chronic course	12	16.7±4.4
	GP, I-II degree, chronic course	48	66.7±5.6
	Generalized catarrhal gingivitis, chronic course	13	5.6±2.7
Comparative group	GP, initial -I degree, chronic course	9	15±4.6
	GP, I-II degree, chronic course	3	5±2.8
	Generalized catarrhal gingivitis, chronic course	35	8.3±3.6
Control group	Almost healthy	30	0

*** - % positive reactions**

No tissue sensitization to bone antigen was established in the patients of the control group. Some peculiarities were observed when analyzing the interdependence of GPD and AN with patients gender, age and their peculiarities of duration, form and stage of the main disease. Thus, no influence of gender on the specific manifestation of GPD, associated with AN, was noticed (Fig. 1)

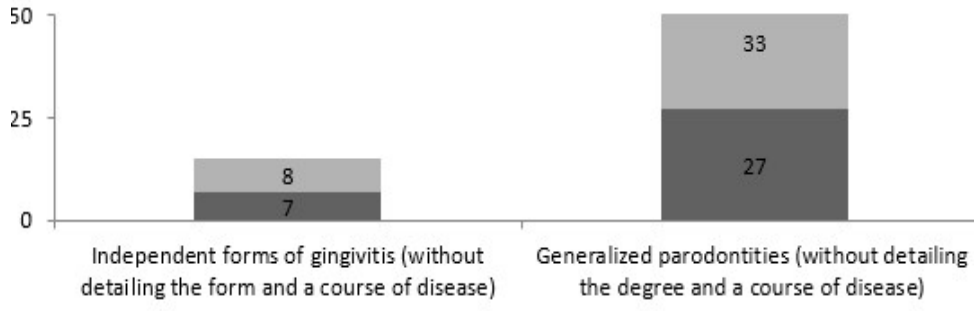

Fig. 1. Impact of the gender of patients with anorexia nervosa on the features of the course of generalized parodontal diseases (abs.)

A high frequency of GPD was defined in all age categories of patients with AN, while the course of GP increased with age (Table 4). Since an exacerbated course of both catarrhal gingivitis and GP was observed in 2 persons, we considered important to analyze the effect of patients' age on the frequency of GPD only among persons with GPD chronic course, associated with AN.

Table 4. Influence of age on the frequency of generalized parodontal diseases in patients with anorexia nervosa

Main disease	Age of patients, years	Catarrhal gingivitis, chronic course	Generalized parodontal diseases	
			GP, initial-I degree, chronic course	GP, I-II degree, chronic course
Anorexia nervosa	18-25	7 9.9±3.5% p > 0.05	8 11.3±3.8% p > 0,05	11 15.5±4.3% p > 0.05
	25-30	4 5.6±2.7% p > 0.05	3 4.3±2.4% P > 0.05	16 22.5±5% p > 0.05
	31-36	2 2.8± 2% p < 0.01	1 1.4±1.4% p > 0.05	18 25.4±5.2% p > 0.05
Total		13 18.3±4.6%	12 17.1±4.5%	45 63.4±5.7%

***p – confidence indicator**

It was established that, as the stages of AN, in particular the primary, anorectic and cachectic ones, progress, the ratio of subjects with GP increases. Thus, if a value of 14.7% was recorded in the initial stage of AN, it reached 20% in the anorectic stage, then it raised to 42.7% in the cachectic stage (Fig.2).

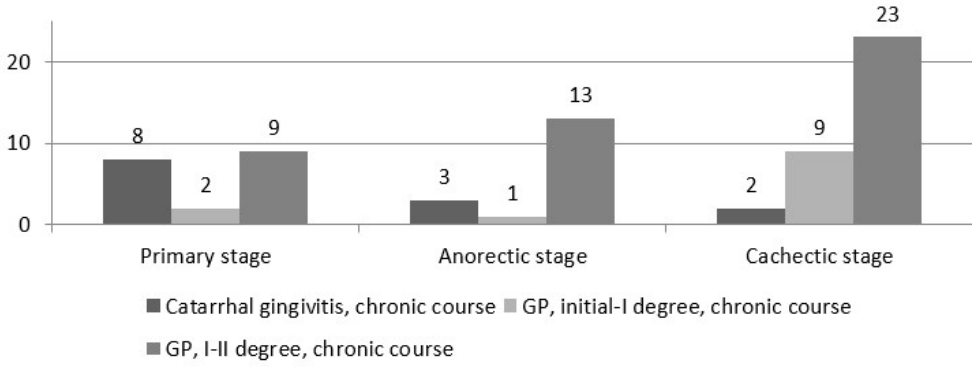

Fig 2. Influence of the stages of anorexia nervosa on the frequency of generalized parodontal diseases (abs.)

The results of the research showed no correlation between the duration of AN and the independent forms of gingivitis, however a direct dependence of the disease and GP was found, more intense for ages between 9 and 12 years (Table 5).

Table 5. Influence of the duration of anorexia nervosa on the manifestation of generalized parodontal diseases

Duration of anorexia nervosa, years	Number of patients	Catarrhal gingivitis, chronic course	Generalized parodontal diseases	
			GP, initial-I degree, chronic course	GP, I-II degree, chronic course
1-3	15	4 5.6±2.7% p > 0.05	3 4.2±2.4% p> 0.05	8 11.3±3.8% p > 0.05

4-8	19	5 7±3% p > 0.05	2 2.9±2% P > 0.05	11 15.5±4.3% P > 0.05
9-12	37	4 5.6±2.7% p < 0.01	7 9.9±3.5% p > 0.05	26 36.6±5.7% p > 0.05
Total		13 18.3±4.6%	12 17.1±4.5%	45 63.4±5.7%

4. CONCLUSIONS

A high incidence of the parodontal disease, reaching 100% in patients with anorexia nervosa, was established. Among the independent forms of gingivitis, the most common was generalized chronic catarrhal gingivitis, more intense on the marginal gums in patients with anorexia nervosa.

Generalized parodontitis prevails over other forms of GPD (80±4.6%), mainly of the I-II degrees, while the chronic course in patients with anorexia nervosa and that of GP depended directly on the age of patients with AN.

The influence of age on the frequency of generalized parodontal diseases has been established. The severity of GP was directly dependent on the age of patients with AN.

The tissue sensitization to bone antigen revealed in patients with GP and AN, even of the initial degree, requires mandatory inclusion in the general treatment regimen of osteotropic drugs, which provide differentiation of cells of the alveolar process and potentiate carbohydrates and the lipid metabolism.

The relationship between the main clinical and radiological manifestations of generalized parodontitis was established according to the duration and stage of nerve anorexia (primary → anorectic → cachectic).

References

1. Borysenko AV, Antonenko MYu., Sidelnikova LF. Practical periodontics: a dentist's guide [in Russian]. Kyiv: Health of Ukraine; 2011.
2. Jagielska GW, Przedlacki J, Bartoszewicz Z, Racicka E. Bone mineralization disorders as a complication of anorexia nervosa - etiology, prevalence, course and treatment. Psychiatr Pol. 2016;50(3):509-20.
3. Mustelin L, Silén Y, Raevuori A, Hoek HW, Kaprio J, Keski-Rahkonen A. The DSM-5 diagnostic criteria for anorexia nervosa may change its population prevalence and prognostic value. J Psychiatr Res. 2016;77:85-91. doi: 10.1016/j.jpsychires.2016.03.003.
4. Goh KH, Lee EL. Prevalence of abnormal liver function tests and comorbid psychiatric disorders among patients with anorexia nervosa and eating disorders not otherwise specified in the anorexia nervosa DSM-IV criteria. Singapore Med J. 2015;56(9):488-92.
5. Hofman M, Landewé-Cleuren S, Wojciechowski F, Kruseman AN. Prevalence and clinical determinants of low bone mineral density in anorexia nervosa. Eur J Intern Med. 2009;20(1):80-4.
6. Cleary BS, Gaudiani JL, Mehler PS. Interpreting the complete blood count in anorexia nervosa. Eat Disord. 2010;18(2):132-9.
7. Spaulding-Barclay MA, Stern J, Mehler PS. Cardiac changes in anorexia nervosa. Cardiol Young. 2016;26(4):623-8.
8. Rosen E, Bakshi N, Watters A, Rosen HR, Mehler PS. Hepatic complications of anorexia nervosa. Dig Dis Sci. 2017;62(11):2977-81.
9. Malczyk Ż, Oświęcimska JM. Gastrointestinal complications and refeeding guidelines in patients with anorexia nervosa. Psychiatr Pol. 2017;51(2):219-29.
10. De Filippo E, Marra M, Alfinito F, Di Guglielmo ML, Majorano P, Cerciello G, et al. Hematological complications in anorexia nervosa. Eur J Clin Nutr. 2016;70(11):1305-8.
11. Norris ML, Harrison ME, Isserlin L, Robinson A, Feder S, Sampson M. Gastrointestinal complications associated with anorexia nervosa: A systematic review. Int J Eat Disord. 2016;49(3):216-37.
12. Mehler PS, Brown C. Anorexia nervosa - medical complications. J Eat Disord. 2015;3:11. doi: 10.1186/s40337-015-0040-8.
13. Stheneur C, Bergeron S, Lapeyraque AL. Renal complications in anorexia nervosa. Eat Weight Disord. 2014;19(4):455-60. doi: 10.1007/s40519-014-0138-z.
14. Brown RF, Bartrop R, Beumont P, Birmingham CL. Bacterial infections in anorexia nervosa: delayed recognition increases complications. Int J Eat Disord. 2005;37(3):261-5.
15. Sudi K, Ottl K, Payerl D, Baumgartl P, Tauschmann K, Müller W. Anorexia athletica. Nutrition. 2004;20(7-8):657-61.

16. Mayhew AJ, Pigeyre M, Couturier J, Meyre D. An evolutionary genetic perspective of eating disorders. Neuroendocrinology. 2018;106(3):292-306. doi: 10.1159/000484525.
17. Ohlrich EJ, Cullinan MP, Seymour GJ. The immunopathogenesis of periodontal disease. Aust Dent J. 2009;54 Suppl 1:S2-10.
18. Hoek HW. Incidence, prevalence and mortality of anorexia nervosa and other eating disorders. Curr Opin Psychiatry. 2006;19(4):389-94.
19. Zaina F, Pesenti F, Persani L, Capodaglio P, Negrini S, Polli N. Prevalence of idiopathic scoliosis in anorexia nervosa patients: results from a cross-sectional study. Eur Spine J. 2018;27(2):293-7.