Časopis Medicinskog fakulteta Univerziteta u Beogradu

UNIVERZITET U BEOGRADU
MEDICINSKI FAKULTET
UNIVERSITY OF BELGRADE
FACULTY OF MEDICINE

Medicinska istraživanja

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[1]Clinical Hospital Centre Bezanijska kosa, Clinic for internal medicine, School of Medicine, University of Belgrade, Belgrade, Serbia
[2]Zemun Clinical Hospital, Clinic for internal medicine, School of Medicine, University of Belgrade, Belgrade, Serbia
[3]Institute for nuclear sciences Vinca, Laboratory for radiobiology and molecular endocrinology, University of Belgrade, Belgrade, Serbia
[4]Clinical Centre Nis, Clinic for endocrinology, School of Medicine, University of Nis, Nis, Serbia
[5]Faculty of Stomatology, Pancevo, University Business Academy, Novi Sad, Serbia

INFLUENCE OF GLYCAEMIA AND HBA1C LEVELS AT ADMISSION OF INSULIN-INDEPENDENT DIABETES PATIENTS ON THE LENGTH AND OUTCOME OF HOSPITALIZATION DUE TO NSTEMI/STEMI

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Summary

This study aims to examine the influence of admission glycaemia and glycosylated haemoglobin (HbA1C) levels on the length of hospitalization and its outcome in insulin-independent diabetes mellitus (DM) patients suffering from ST-Segment Elevation Myocardial Infarction (STEMI)/Non-STEMI (NSTEMI).

This cross-sectional study included 103 subjects with a history of insulin-independent DM, currently hospitalized due to acute myocardial infarction (AMI). Out of 103 subjects, 59 (57%) were men and 66 (64.1%) of them suffered from STEMI. Mean age of study population was 67±9 years. The following parameters were monitored: demographic, coronary, cardiovascular and DM risk factors history, as well as laboratory, clinical, echocardiography and angiography parameters.

DM mean duration was 7 (1-30) months, and it influenced the length of hospitalization ($\rho=0.232$, $p<0.05$), but not the outcome ($\rho=0.174$, $p>0.05$). Mean length of hospitalization was 8 and 8.5 days in STEMI and NSTEMI patients respectively, with no difference between groups (log-rank $\chi2= 0.476$, $p>0.05$). HbA1C values influenced the length of hospitalization ($\rho=0.213$, $p<0.05$), opposite to admission glycaemia ($\rho=0.148$, $p>0.05$).

Duration of DM and the level of HbA1C prolong the length of hospitalization, but do not influence the clinical outcome of AMI patients suffering from insulin-independent DM.

Key words: acute myocardial infarction, diabetes, glycaemia, HbA1C

Sažetak

Cilj prikazane studije je izučavanje uticaja glikemije i glikoziliranog hemoglobina (HbA1C) pri prijemu u bolnicu na dužinu trajanja hospitalizacije, kao i njen ishod kod kod obolelih od insulin-nezavisnog dijabetesa sa NSTEMI/STEMI.

Materijal i metode: Ova studija je uključila 103 ispitanika, od kojih su 59 (57%) ispitanici muškog pola, a 66 (64.1%) ispitanika imalo STEMI. Prosečna životna dob ispitivane populacije je bila 67±9 godina. Praćeni su sledeći parametri: demografske karakteristike, anamneza o koronarnim, kardiovaskularnim i rizičnim faktorima za dijabetes, kao i laboratorijski, klinički, ehokardiografski parametri.

Rezultati: Prosečno trajanje dijabetesa kod osoba uključenih u studiju je bilo 7 (1-30) meseci i imalo je uticaj na dužinu hospitalizacije ($\rho=0.232$, $p<0.05$), ali ne i na njen krajnji ishod ($\rho=0.174$, $p>0.05$). Prosečno trajanje hospitalizacije je bilo 8 i 8.5 dana kod ispitanika sa STEMI i NSTEMI i nije se razlikovalo među grupama ispitanika (log-rank $\chi2= 0.476$, $p>0.05$). Nivoi HbA1C su uticali na dužinu trajanja hospitalizacije ($\rho=0.213$, $p<0.05$), što nije bio slučaj sa glikemijom pri prijemu u bolnicu ($\rho=0.148$, $p>0.05$).

Zaključak: Dužina trajanja DM i nivo HbA1C produžavaju dužinu hospitalizacije, ali ne utiču na klinički ishod ispitanika sa insulin-nezavisnim dijabetesom koji su doživeli AIM.

Ključne reči: akutni infarkt miokarda, dijabetes, glikemija, Hba1C

INTRODUCTION

Acute myocardial infarction (AMI) is a clinical form of coronary heart disease, which occurs during occlusion of the coronary artery and is histologically defined as myocardial necrosis [1]. Diabetes mellitus (DM) is a metabolism disorder of carbohydrates, fats and proteins induced by absolute or relative insulin deficiency. The phenomenon of accelerated atherosclerosis, as the essence of DM, is caused by co-action of genetic and non-genetic factors which lead to serious cardio-, cerebral- and peripheral vascular morbidity. This phenomenon dominates in small blood vessels in type 1 DM as well in macrovascular circulation in type 2 DM (2, 3). More than 60% of DM patients die from vascular complications, whereby mortality rate of DM patients suffering from AMI and acute brain stroke is 2-4 times higher than in persons not suffering from DM. An acute disturbance in glycaemia often follows AMI, rarely presented as diabetic ketoacidosis. Poor glycemic control associated with an

acute coronary event almost always deranges glycosylated haemoglobin (HbA1C) levels (4-6).

This study aims to present epidemiological, clinical and angiographic features of ST-Segment Elevation Myocardial Infarction (STEMI)/Non-STEMI (NSTEMI) in insulin-independent DM patients, as well as the effect of hospital admission glycaemia and Hb1C levels on the length and outcome of hospitalization.

MATERIAL AND METHODS

This cross-sectional study included 103 subjects, who were hospitalized at the Coronary Care Unit of University Hospital Medical Center (UHMC) Bezanijska Kosa due to the AIM with STEMI (66 subjects) or AIM without ST elevation (NSTEMI) (37 subjects), with already diagnosed and treated insulin-independent DM. The exclusion criteria were the previous insulin treatment, recent coronary event (within 6 months), invasive and surgical treatment of heart or other diseases surgically managed (all requiring temporary or permanent insulin treatment).

The following parameters were monitored: demographic (sex, age), previous risk factors history (for coronary and cardiovascular disease as well as DM), laboratory (haematological and biochemical), clinical (signs of heart failure (HF), arterial blood pressure, presence of rhythm or conduction disorders, length of hospitalization, outcome of disease), as well as echocardiography and angiography findings.

Local Ethic Committee approved the study. A written agreement of subjects to the mentioned invasive procedure was taken as mandatory.

HAEMATOLOGY ANALYSIS

Haemoglobin level was determined on Pentra 120 micros 60 analyser (HORIBA ABX SAS, Kyoto, Japan) and values are expressed in g/L.

BIOCHEMICAL ANALYSIS

Measurement of plasma glucose

Admission plasma glucose levels were measured by a standardized GLUC-PAP method on Roche Cobas c 501 analyzers (Roche Diagnostics, Indianapolis, USA), according to the m7. nufacturer's guidelines. Level of glycaemia is expressed in mmol/l.

Measurement of HbA1C

The specific measurement of HbA1C was carried out using an immunological method with an antibody to the beta chain of HbA1C, on Roche Cobas c 501 analyser (Roche Diagnostics, Indianapolis, USA). The HbA1C test result is reported as a percentage (%).

Measurement of creatine kinase (CK)

The concentration of CK was measured using *in vitro* test for quantitative determination of CK MB subunit (CK-MB) catalytic activity in human serum, on Roche Cobas c 501 analyzer (Roche Diagnostics, Indianapolis, USA). The CK activity in the sample is expressed in U/L.

Measurement of troponin T

The concentration of troponin T values was measured on automated VIDAS® instrument, following manufacturer's guidelines, using the enzyme-linked fluorescent immunoassay, VIDAS Troponin I Ultra assay (bioMérieux, Marcy L'Etoile, France). Troponin T concentration is expressed in ng/ml.

Measurement of creatinine concentration

The measurement of creatinine was carried on Roche Cobas c 501 analyzer (Roche Diagnostics, Indianapolis, USA). The creatinine concentration was expressed in μmol/L.

Measurement of serum potassium ion concentration

The concentration of potassium ion in serum was determined on Roche Cobas c 501 analyzer (Roche Diagnostics, Indianapolis, USA). Briefly, this method determines potassium ion concentration by indirect potentiometry using a potassium ion selective electrode. The potassium ion concentration is expressed in mmol/l.

Measurement of triglycerides (TC) and total LDL and HDL cholesterol concentration

The concentration of TG was measured using a commercially available kit according to the manufacturer's guidelines, carried on a Roche Cobas c 501 analyzer (Roche Diagnostics, Indianapolis, USA). Total cholesterol was determined by standardized enzymatic colour test (enzymatic assay), using cholesterol oxidase-peroxidase enzyme. The values of LDL were calculated using Friedewald's equation.

$$LDL = \text{total cholesterol} - HDL - 0.45 \times TG \text{ [mmol/l]}$$

HDL-cholesterol was determined by the precipitation method with sodium phosphowolframate. LDL and HDL cholesterol concentrations were expressed in mmol/l.

Measurement of Serum C-reactive protein (CRP) Concentration

The concentration of CRP in serum was measured by the immunoturbidimetric method using a commercially available kit (System reagent for the quantitative determination of CRP in human serum), following manufacturer guidelines, on Roche Cobas c 501 analy-

ser (Roche Diagnostics, Indianapolis, USA). The results were expressed in ng/L.

CLINICAL, ECHOCARDIOGRAPHY AND ANGIOGRAPHY PARAMETERS

Clinical parameters (HF signs), as well as the presence of rhythm and/or conduction disorders (as electrocardiogram-ECG), were monitored and registered upon the admission of subjects. Measuring of systolic and diastolic pressure was done with a *Riestar precisa* manometer and values were displayed in a millimetre mercury (mmHg) column. *ECG* was recorded with *Nihon Kohden Cardiofix gem*, on a 25mm paper. An ejection fraction (in %) was registered with the echocardiographic examination, conducted on *Vivid 4 device*, as well as the presence of wall kinetic disorders, presented as akinesia and hypokinesia. Angiography finding described left coronary artery (LCA) and/or left anterior descending (LAD) stenosis in %, as well as precise location of an acute lesion (expressed as stenosis in %). Angiography was conducted at UHMC Bezanijska Kosa.

STATISTICAL METHODOLOGY

Methods of descriptive (relative numbers, central tendency and variability measures) and analytical statistics were used. Regarding the analytical statistics methods, tests for assessment of correlation significance (Spearman rank correlation test) and difference (χ^2 and Mann-Whitney test) were used. The Kaplan-Meier survival curve was used for calculating the length of hospitalization per groups of subjects in relation to the outcome of a disease; the comparisons of obtained values were performed by a Log-rank test. Level of statistical significance was 0.05.

RESULTS

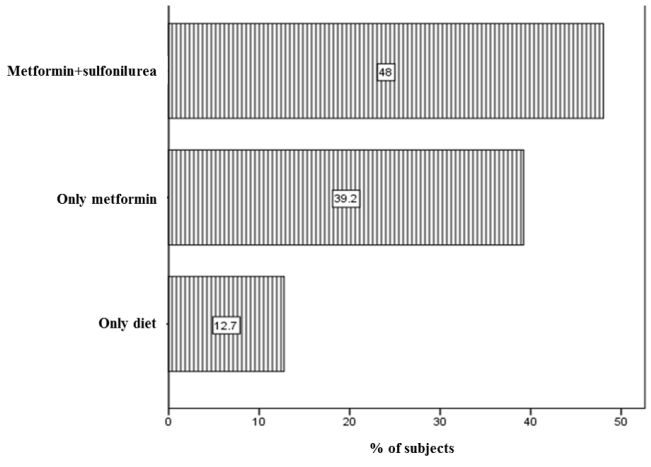
The average age of study subjects was 67±9 (46-92 years) and did not differ between groups (Z=-0.389, p>0.05). Results show that age influenced the length of hospitalization (ρ=0.261, p<0.01). No statistically significant difference in the distribution of subjects per groups according to the gender was registered (χ^2=0.246, DF=1, p>0.05).

Clinical parameters of the studied subjects' are presented in Table 1. The difference was registered in the case of HF presence (χ^2=5.117, DF=1, p<0.05). No significant differences in other observed parameters among studied groups were registered (subjects distribution per Killip classification, the presence of rhythm and conduction disorders). Average systolic and diastolic pressures were 149±31 and 83±16 mmHg and did not differ between groups. Out of 46 subjects with a HF, STEMI and NSTEMI were registered in 24 and 22 participants, respectively. The presence of HF influenced the hospitalization outcome (ρ=-0.290, p<0.05). Five (5%) subjects have had a family history for presence of DM, while 8 (8%) subjects have had the family presence of DM and cardiovascular/coronary disease simultaneously. The median duration of DM in patients with STEMI and NSTEMI was 7 months, which was also the duration of DM treatment. Duration of DM had a significant influence on the length of current hospital treatment of the patients (ρ=0.232, p<0.05), but not on the outcome of the disease (ρ=0.174, p>0.05). Results presented in Fig. 1 shows that there were no differences among groups of subjects with regards to different DM treatment modalities (χ^2=0.464, DF=2, p>0.05).

Table 1. Clinical parameters

Parameter	n (%)
Heart Failure	46 (44.7)
Killip classification	I - 9 (19.6) II - 30 (65.2) III - 3 (6.5) IV - 4 (8.7)
Rhythm disorder	25 (24.3)
Conduction disorder	4 (3.9)

Figure 1. Treatment modalities of DM



The analysis of risk factors for coronary/cardiovascular diseases revealed 40 (39%) active and 16 (15%) former smokers. Also, dyslipidaemia (regardless of whether it was treated or not) was present in 54 (52.4%) subjects. The previous history of coronary/cardiovascular disease was documented in 49 (47.6%) examinees.

Regarding echocardiography, average EF was 40±10 (15-60%) and did not differ between groups (t=0.752, DF=101, p>0.05). The disorders of wall kinetics were detected in 99 (96%) subjects: akinesia and dyskinesia in 73 (71%) and 26 (25%) subjects. Angiography-detected stenosis on LCA and LAD was registered in 20 (19%) and 86 (83%) subjects, with average stenosis of 70 (20-96) and 83 (30-100) %. Acute lesion and, at the same time, the place of stent insertion, was localized in LAD, circumflex coronary artery (ACx) and right coronary

artery (RCA) in 42 (40%), 23 (22%) and 35 (34%) subjects respectively, with average stenosis of 95±5 (75-100) %. Table 2 presents results of average initial values of laboratory parameters in the observed population.

Table 2. Initial hematological and biochemical parameters

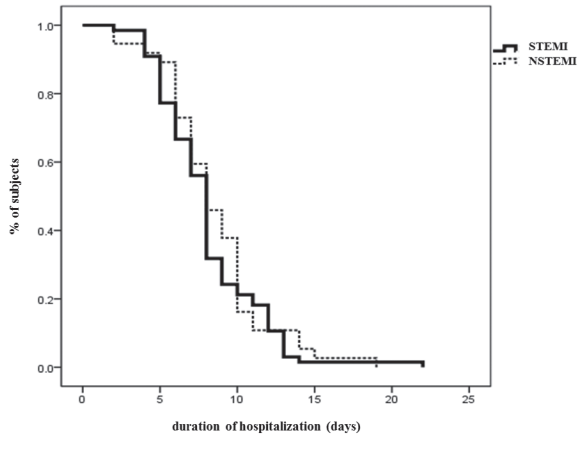
Parameter	Average value
Glycaemia - mmol/L [Med]	10.9 (4.5-37.0)
HbA1C - % [Mean]	7.4±1.6
CK - U/L [Med]	171 (40-1807)
Troponin - ng/ml [Med]	0.63 (0.01-30.0)
Total cholesterol - mmol/L [Mean]	5.5±1.3
LDL cholesterol - mmol/L [Mean]	3.4±0.9
HDL cholesterol - mmol/L [Med]	1.0 (0.5-3.8)
TG - mmol/L [Med]	2.0 (0.6-16.8)
Hemoglobin - g/L [n (%)]	<100 – 5 (5) ≥100 – 98 (95)
Potassium - mmol/L [Mean]	4.4±0.5
Creatinine - µmol/L [Med]	95 (38-479)
CRP - ng/L [Med]	8.7 (0.01-270)

Abbreviations: HbA1C - Glycosylated Haemoglobin; CK - Creatine Kinase; LDL - Low-density lipoprotein; HDL - High-density lipoprotein; TG – Triglyceride CRP - C-reactive protein

The average length of hospitalization was 8.25 (2-22) days. In subjects with STEMI and NSTEMI it was 8 and 8.5 days, and it did not differ between groups (log-rank χ^2=0.476, p>0.05) (Fig. 2). Admission glycaemia level did not have a significant effect on length of hospitalization (ρ_{gly}=0.148, p>0.05), as opposed to HbA1C levels (ρ_{HbA1C}=0.213, p<0.05).

Out of the total number of subjects, four (3.9%) died at the hospital, three of those subjects had STEMI, and one had NSTEMI. With regards to the outcome of the disease, no statistically significant difference between examined groups was detected (χ^2=0.216, DF=1, p>0.05). Admission glycaemia and HbA1C level did not influence the outcome of the disease (ρ_{gly}=0.165, ρ_{HbA1C}=0.047, p>0.05).

Figure 2. Kaplan-Meier curve for the length of hospitalization in both outcomes of the disease with regard groups of subjects



Abbreviation: STEMI - ST-Segment Elevation Myocardial Infarction; NSTEMI - Non-STEMI

In Table 3, some of the demographic, previous history and clinical parameters were presented, whereas Table 4 shows frequency distribution of subjects according to the types of DM treatment, and laboratory parameters per group of subjects were presented in Table 5.

Table 3. Demographic, previous history and clinical parameters per group of subjects

Parameter	STEMI (n= 66)	NSTEMI (n= 37)
Male gender [n (%)]	39 (59)	20 (54)
Age [Mean]	67±9	67±9
Smoking habit [yes (%)]	27 (41)	13 (35)
Positivehistory of dyslipidemia [yes(%)]	30 (45)	24 (65)
Positive family history of dyslipidemia [yes (%)]: • coronary/cardiovascular disease • DM • coronary/cardiovascular disease + DM	30 (45) 3 (5) 4 (6)	19 (51) 2 (5) 4 (11)
HF [yes (%)]	24 (36)	22 (60)
Rhythm disorders [yes (%)]	12 (18)	13 (25)
Conduction disorders [yes (%)]	3 (4)	1 (3)

Abbreviations: HF - Hart Failure; DM - Diabetes Mellitus

Table 4. The frequency distribution of subjects by DM treatment modalities

Therapeutic modalities	STEMI	NSTEMI
Non-pharmacological [yes (%)]	10 (15)	4 (11)
Metformin [yes (%)]	24 (36)	16 (43)
Metformin + sulfonylurea [yes (%)]	32 (49)	17 (46)

Abbreviations: STEMI - ST-Segment Elevation Myocardial Infarction; NSTEMI - Non-STEMI

Table 5. The hematological and biochemical parameters in groups of studied subjects

Parameter	STEMI	NSTEMI	p
Glycemia - mmol/L [Med]	11.7 (4.5-37.0)	10.3 (6.4-34.0)	ns
HbA1C - % [Mean]	7.4±1.6	7.4±1.5	ns
CK - U/L [Med]	172 (42-1807)	171 (40-1636)	ns
Troponin - ng/ml [Med]	0.88 (0.01-30.0)	0.56 (0.01-4.3)	ns
Total cholesterol - mmol/L [Mean]	5.4±1.2	5.7±1.4	ns
LDL cholesterol - mmol/L [Mean]	3.3±0.9	3.6±1.1	ns
HDL cholesterol - mmol/L [Mean]	1.0 (0.4-3.8)	0.9 (0.6-1.8)	ns
TG - mmol/L [Med]	1.9 (0.6-16.8)	2.2 (0.7-8.6)	ns
Hemoglobin - g/L [n (%)]	<100 – 4 (6) ≥100 – 62 (94)	<100 – 1 (3) ≥100 – 36 (97)	ns
Potassium - mmol/L [Mean]	4.4±0.5	4.4±0.5	ns
Creatinine - µmol/L [Med]	96 (40-203)	87 (38-479)	ns
CRP - ng/L [Med]	8 (0.4-270)	10 (0.0-103)	ns

Abbreviations: HbA1C - Glycosylated Haemoglobin; CK - Creatine Kinase; LDL - Low-density lipoprotein; HDL - High-density lipoprotein; TG – Triglyceride; CRP - C-reactive protein; STEMI - ST-Segment Elevation Myocardial Infarction; NSTEMI - Non-STEMI

DISCUSSION

In the presented cross-sectional study, 103 subjects treated for insulin-independent DM, were hospitalized due to an acute coronary event, STEMI and NSTEMI. Influence of admission glycaemia on the length and outcome of hospitalization was not registered. Also, duration of DM and the level of HbA1C did not have significant effects on the current treatment outcome but prolonged the average length of hospitalization, which was not statistically different between studied groups.

Cardiovascular morbidity and mortality in patients suffering from insulin-independent DM is 2-5 times higher than in age-matched non diabetic persons (6). According to the GUSTO study, in-hospital mortality in DM patients was 10.6%, and 6.2% in non-diabetic patients (7), which is not significantly different from overall mortality rate in our study (4%). About 75% of patients suffering from insulin-independent DM die due to some macrovascular complication (coronary, peripheral or cerebrovascular disease). Cardiovascular disease is responsible for death of 75% patients suffering from insulin-independent, and 35% patients suffering from insulin-dependent DM (8).

Lipid profiles in our study population indicated mixed dyslipidaemia, increased level of LDL cholesterol and borderline protective level of HDL cholesterol. According to the United Kingdom Prospective Diabetes Study (UKPDS), the main risk factors for coronary disease in insulin-independent DM patients are increased LDL cholesterol, reduced HDL cholesterol, associated with the presence of hypertension, hyperglycaemia, and smoking (9). Almost half of the study subjects were former/present smokers, with concomitant presence of dyslipidaemia or any CVD, while less than 10% of subjects had a family history for DM and CVD. The most prevalent risk factors for CVD in DM patients, regardless of the type, were still hypertension and dyslipidaemia, whereby DM itself was also an independent risk factor. So, all of already mentioned support the fact of an extreme importance of primary and secondary prevention in DM and CVD (6,9).

In our study, even mild increase in average CRP values that were significantly different among the examined groups indicated a presence of inflammation, which forms the basis of atherosclerosis (10). Additionally, the increased average systolic arterial pressure in our study also contributed to the acceleration of observed atherosclerosis (2,4). The presence of HF additionally contributed to higher mortality rates due to the acute coronary syndrome in diabetes patients (3,7,9). In our study, 46 (44.7%) subjects had HF after an acute coronary event, slight frequently registered in patients suffering from STEMI. HF might also be considered as ominous sign in DM patients with an acute coronary syndrome (7,9).

Coronary heart disease in DM patients occurs at an earlier age in comparison to subjects who are not suffering from DM. There are more patients susceptible to complications and unfavourable outcomes in diabetes patients with coronary heart disease. An explanation for this could be in extension of atherosclerosis process as well as in somehow late reporting to physicians considering atypical disease presentation even clinically silent, because of autonomic neuropathy (6). Even though the duration of DM was relatively short (7 months on average in present study), patients were much earlier aware of hyperglycemia existence, but usually further tests considering the presence of DM and its complications were not undertaken. For this reason, the time of DM diagnosis setting sometimes coincides with the start of DM treatment (3).

In patients suffering from STEMI, primary coronary intervention is a management method of choice. By using drug-eluting stents, a better outcome quality is achieved regarding the reduction of some restenoses, long-term recovery, as well as a decrease in frequency of surgical revascularization (6, 11-13). Morphologically, atherosclerotic changes in coronary arteries in DM patients are diffuse, more extensive, frequently on two or three coronary blood vessels, usually unfavourable for dilatation (12). Hyperglycaemia and insulin resistance favour endothelial dysfunction, prothrombogenic state, protein glycosylation and vascular matrix deposition. Therefore, patients with DM and AIM have an increased risk of the unfavorable outcome of a percutaneous coronary intervention when compared to non-diabetic patients. Greater possibility of early in-stent thrombosis, restenosis, as well as negative vascular remodeling contributes to such outcome (14,15). In present study, surgical revascularization was proposed in 40% of subjects, and this is in concordance with recommendations (6,16).

Though they already suffered from DM, some of acute coronary patients ignore DM as disease (5,8). Despite the low mortality rate from coronary disease in insulin-independent DM patients in this study, it is necessary once again to emphasize the importance of primary and secondary prevention of the coronary disease risk factors.

In conclusion, the results from this cross-sectional study did not show difference among groups regarding the length of hospitalization and its outcome in insulin-independent DM subjects, currently hospitalized due to NSTEMI or STEMI. Higher levels of HbA1C extended the duration of hospital treatment of coronary disease, which was not the case with admission glycaemia level. Acute and retroactive glycometabolic regulation did not influence the in-hospital outcomes of the disease in the observed population.

Acknowledgements

This study was partially funded by the grant (No. 173033) to E.R.I. from the Ministry of Science, Republic of Serbia.

Compliance with ethical standards

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

REFERENCES

1. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, the Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551–67.
2. Gregg EW, Li Y, Wang J, Burrows NR, Ali MK, Rolka D, et al. Changes in diabetes-related complications in the United States. 1990–2010. N Engl J Me 2014;370:1514–23.
3. Desai JR, Vazquez-Benitez G, Xu Z, Schroeder EB, Karter AJ, Steiner JF, et al. Who Must We Target Now to Minimize Future Cardiovascular Events and Total Mortality? Lessons from the Surveillance, Prevention and Management of Diabetes Mellitus (SUPREME-DM) Cohort Study. Circ Cardiovasc Qual Outcomes 2015; 8:508-16.
4. Luscher TF, Creager MA, Beckman JA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequence and medical therapy: Part II. Circulation. 2003; 108:1655-61.
5. Fonseca VA. Risk factors for coronary heart disease in diabetes. Ann Intern Me 2000; 133(2):154-56.
6. Dandona P, Chaudhuri A. Diabetes: glycaemia and insulin after acute myocardial infarction. Nat Rev Endocrinol 2014; 10:448-50.
7. The GUSTO investigators. An international randomized trial compares four thrombolytic strategies for acute myocardial infarction. NEJM 1993; 329(10):673-82.
8. Preis SR, Pencina MJ, Hwang SJ, D'Agostino RB Sr., Savage PJ, Levy D, et al. Trends in cardiovascular disease risk factors in individuals with and without diabetes mellitus in the Framingham Heart Study. Circulation 2009; 120:212–20.
9. Turner RC, Millns N, Neil HA, Stratton IM, Manley SE, Matthews DR, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: UKPDS 23. BMJ 1998; 316:823-28.
10. Danesh J, Wheeler JG, Hirschfield GM, Gideon M, Eiriksdottir G, Rumley A, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. NEJM 2004; 350:1387-97.
11. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). Eur Heart J 2012; 33:2569-19.
12. Pajuenen O, Taskinen MR, Nieminen MS, Syvanne M. Angiography severity and extent of coronary artery disease in patients with type 1 diabetes mellitus. Am J Cardiol 2000; 86(10):1080-85.
13. Malberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at one year. J Am Coll Cardiol 1995; 26(1):57-65.
14. Waller B, Palumbo P, Roberts W. Status of the coronary arteries at necropsy in diabetes mellitus with onset after age 30 years. Is J Med 1980; 69:498-506?
15. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. NEJM 2001; 344(25):1879-87.
16. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37:267-315.

[1]Institut za onkologiju i radiologiju Srbije, Beograd, Srbija
[2]Medicinski fakultet, Univerzitet u Beogradu, Beograd, Srbija

EXPERIENCE OF THE INSTITUTE OF ONCOLOGY AND RADIOLOGY OF SERBIA IN RADIOTHERAPY TREATMENT OF MALIGNANT TUMORS IN CHILDREN

ISKUSTVO INSTITUTA ZA ONKOLOGIJU I RADIOLOGIJU SRBIJE U RADIOTERAPIJSKOM LEČENJU MALIGNIH TUMORA DECE

Dragana Stanić[1], Jelena Bokun[1], Marina Nikitović[1,2]

Summary

The Institute of Oncology and Radiology of Serbia in Belgrade is an institution in which the implementation of radiotherapy of children and adolescents started 35 years ago. To date, pediatric radiotherapy has been set up and has been following technological possibilities and progress, and a highly specialized multidisciplinary team has been established in the institution with a focus on pediatric oncology and radiotherapy. Purchase of equipment for three-dimensional conformal radiotherapy (3D-CRT) in 2006 enabled qualitative progress in the planning and implementation of pediatric radiotherapy.

60 to 80 patients aged 1 to 18 years are treated annually in our institution. For children aged up to 3 years, and in extremely rare cases older, radiotherapy is carried out in anesthesia, which is emphasized as a significant experience and quality of work of our institution. In the ten-year period from January 2007 to September 2016, 648 children were treated with radiotherapy. In the majority of children, 90.6%, radiotherapy was conducted using 3D conformal technique (3D-CRT) and in small number, 9.4% with conventional radiotherapy (2D-RT). The most frequent patients were children with central nervous system tumors 30.1%, leukemia 16.5%, bone tumors 15.4%, lymphoma 11.9%, soft tissue sarcoma 11.6%, neuroblastoma 6.5%, nephroblastoma 3.6%, retinoblastoma 1.7% and other rare tumors. Besides operative treatment, the majority of children were treated with chemotherapy and radiotherapy, 89.8%. Most of the children treated with radiotherapy were treated with chemotherapy in our institution, 45.8%. In a small number of children, radiotherapy was conducted as the only therapeutic approach, 10.2%.

At the Institute for Oncology and Radiology of Serbia, as a central institution for pediatric radiotherapy, 3D-CRT has been fully adopted as a standard in the treatment of children and adolescents. In the past ten years, we have gained our own experiences which will be of great use to us with introduction of advanced techniques that we expect to gain by further purchase of machines and equipment for radiotherapy.

Key words: radiotherapy, pediatric oncology

Sažetak

Institut za onkologiju i radiologiju Srbije u Beogradu je ustanova u kojoj je pre 35 godina započeto sprovođenje zračne terapije kod dece i omladine. Do danas je osnovana pedijatrijska radioterapija koja se razvijala, pratila tehnološke mogućnosti i napredak, a u ustanovi se formirao visokospecijalizovan multidisciplinarni tim sa usmerenjem ka pedijatrijskoj onkologiji i radioterapiji. Kupovinom opreme za trodimenzionalnu konformalnu radioterapiju (3D-CRT) 2006. godine omogućen je kvalitativni napredak u planiranju i sprovođenju pedijatrijske radioterapije.

Godišnje se zračnom terapijom u našoj ustanovi leči 60 do 80 pacijenata uzrasta od 1 do 18 godina. Za decu uzrasta do 3 godine, izuzetno retko i stariju, zračna terapija se sprovodi u anesteziji što ističemo kao značajno iskustvo i kvalitet rada naše ustanove. U desetogodišnjem periodu od januara 2007. do septembra 2016. godine radioterapijom je lečeno 648 dece. Kod najvećeg broja dece, 90.6%, sprovodena je zračna terapija upotrebom 3D konfomalne tehnike (3D-CRT), a kod malog broja, 9.4% konvencionalnom radioterapijom (2D-RT). Najčešći pacijenti bili su deca sa tumorima centralnog nervnog sistema 30.1%, leukemijom 16.5%, koštanim tumorima 15.4%, limfomima 11.9%, mekotkivnim sarkomima 11.6%, neuroblastomom 6.5%, nefroblastomom 3.6%, retinoblastomom 1.7% i ostalim retkim tumorima. Uz operativno lečenje najveći broj dece lečen je hemioterapijom i radioterapijom, 89.8%. Većina dece kod kojih je sprovedena radioterapija lečena je hemioterapijom u našoj ustanovi, 45.8%. Kod malog broja dece sprovedena je radioterapija kao jedini terapijski pristup, 10.2%.

U Institutu za onkologiju i radiologiju Srbije, kao centralnoj ustanovi za pedijatrijsku radioterapiju, u potpunosti je usvojena 3D-CRT kao standard u lečenju dece i omladine. U proteklom desetogodišnjem periodu stekli smo sopstvena iskustva koja će nam biti od velike koristi prilikom uvođenja naprednijih tehnika koje očekujemo daljom kupovinom uređaja i opreme za radioterapiju.

Ključne reči: radioterapija, pedijatrijska onkologija

UVOD

Radioterapijski tretman u pedijatrijskoj onkologiji predstavlja veći izazov u odnosu na lečenje odraslih. Velika većina dece se leči kurativnom pristupom za veliki broj maligniteta, od kojih su mnogi ili retki ili ne postoje kod odraslih. Pored toga, tkiva dece imaju manju toleranciju prema zračenju nego tkiva odraslih, a u mnogim slučajevima deca imaju relativno velike ciljne volumene zračenja, koji u zavisnosti od dijagnoze, zahtevaju značajne

doze (1). Suprotno uobičajenom verovanju, mala deca obično nemaju male tumore. Još jedna razlika u pedijatrijskoj radijacionoj onkologiji je u tome što, za razliku od odraslih, deca često primaju konkomitantnu hemioterapiju. Ovo dodatno smanjuje toleranciju određenih tkiva, na primer, povećava ototoksičnost cisplatine ili toksičnosti antraciklina (2).

Institut za onkologiju i radiologiju Srbije (IORS) u Beogradu je ustanova u kojoj je pre 35 godina započeto sprovođenje zračne terapije kod dece i omladine. Do danas je osnovana pedijatrijska radioterapija koja se razvijala, pratila tehnološke mogućnosti i napredak, a u ustanovi se formirao visokospecijalizovan multidisciplinarni tim sa usmerenjem ka pedijatrijskoj onkologiji i radioterapiji.

Kupovinom opreme za trodimenzionalnu konformalnu radioterapiju (3D-CRT) 2006. godine omogućen je kvalitativni napredak u planiranju i sprovođenju pedijatrijske radioterapije (3). Termin konfomalna radioterapija podrazumeva primenu tehnika zračenja čijim se korišćenjem dobija distribucija doze prilagođena obliku ciljnog volumena, što omogućava precizno aplikovanje terapijske doze na tumor, uz maskimalnu poštedu okolnih zdravih struktura. Ovaj napredak u kvalitetu radioterapije zasnovan je na napretku kompjuterske tehnologije, primeni savremenih imidžing metoda (CT, MR), konstruisanju pouzdanih radioterapijskih uređaja i kompjuterskih sistema za planiranje zračenja. Glavna razlika u odnosu na konvencionalnu radioterapiju (2D-RT) predstavlja korišćenje više zračnih snopova i rezultujuća trodimenzionalna distribucija doze dobijena putem CT simulacije pacijenta.

Pri radioterapiji dece, čiji se organizam nalazi u periodu rasta i razvoja, korišćnje 3D-CRT je od posebnog značaja (4). Na primer, kod dece se mora voditi računa o simetričnom ozračivanju aksijalnog skeleta. U suprotnom, asimetričan rast može dovesti do velikih deformiteta. Kada tretiramo mete koje se nalaze blizu kičme dece, moramo povećati zračna polja kako bi ravnomerno tretirali celo pršljensko telo, da se ne bi prouzrokovao asimetričan zastoj u rastu. Kod dece rast kostiju je zaustavljen ako je data doza veća od 18 Gy. Neke strukture su od ključnog značaja za zaštitu kod dece, dok se u velikoj meri ignorišu u radioterapiji odraslih. Primer je efekat zastoja u rastu dece kada se hipofiza tretira sa više od oko 20 Gy zbog posledičnog smanjenja lučenja hormona rasta. Takođe kod dece, doze na jajnike i testise veće od 5 do 10 Gy mogu prouzrokovati neplodnost deteta, dok odrasli koji su završili svoj reproduktuvni period nisu izloženi riziku od istih doza. Organi koji se mogu oštetiti pri manjim dozama kod dece u odnosu na odrasle, ili su od interesa zbog dužeg vremena tokom koga se toksičnost može manifestovati, uključuju i srce, karotidne i druge arterije, kao i mozak. U palijativne svrhe, 30 do 36 Gy se daje odraslima sa metastazama u mozgu bez većih kognitivnih efekata; međutim, ova doza data trogodišnjem detetu nosi sa sobom poražavajuće posledice.

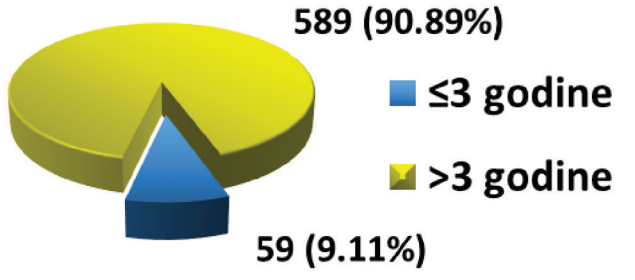
Dodatno praktično razmatranje pri radioterapiji pedijatrijske poplacije je da je deci mlađoj od 3 ili 5 godina, ponekad i starijoj, potreban tretman u sedaciji ili opštoj anesteziji. Svakodnevna sedacija u trajanju od nekoliko nedelja bezbedno se izvodi čak i kada period sedacije traje do sat vremena ili više. Anesteziolog mora biti prisutan da upravlja procesom i prati bolesnika. Često, kako bi se postigla optimalna ventilacija tokom anestezije, dečija brada mora biti podignuta i zadržana u ovom položaju. Prilikom pravljenja sredstava za imobilizaciju glave, ekstenzija brade se mora uzeti u obzir.

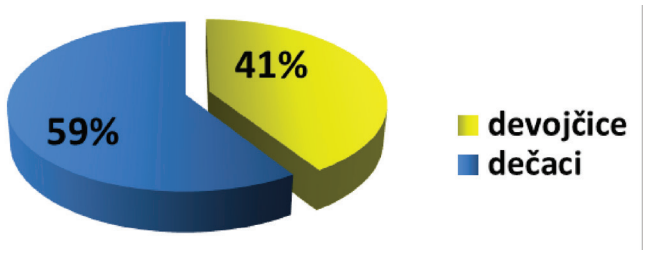
Još jedan važan faktor koji treba uzei u obzir prilikom planiranja zračnog tertmana dece je to da je rizik za pojavu sekundarnih maligniteta izazvanih zračenjem veći kod dece nego kod odraslih. Ovo je možda posledica povećane osetljivosti normalnog tkiva na mutagene efekte zračenja u mlađem uzrastu, veće proliferacije ćelija u ranim stadijumima rasta i razvoja ili genetskih promena povezanih i sa pojavom primarnog maligniteta (5). Dete koje preživi primarni tretman ima mnogo godina pred sobom u kojima može da razvije drugi malignitet.

O svemu navedenom se vodi računa prilikom radioterapijskog tretmana dece u IORS.

Grafikon 1. Distribucija dece prema uzrastu

Grafikon 2. Distribucija dece prema polu





TUMORI CENTRALNOG NERVNOG SISTEMA

Tumori centralnog nervnog sistema (CNS) čine oko 20% do 25% svih maligniteta koje se javljaju u detinjstvu. Moždani tumori su najčešći solidni tumori u pedijatrijskom dobu i posle leukemija čine najčešću grupu maligniteta (6). Za razliku od odraslog doba, u pedija-

trijskoj populaciji primarni tumori mozga su mnogo češći od metastaza.

Većina moždanih tumora se širi lokalno, u okolno moždano tkivo. Metastaze za moždane tumore uključuju širenje duž neuralne osovine i ekstraneuralne metastaze. Širenje neuralnom osovinom je osobina koju imaju meduloblastomi, ependimomi, tumori germinativnih ćelija i supratentorijalni embrionalni tumori. Oko 30-40% meduloblastoma ima diseminaciju prilikom dijagnoze (7). Ependimomi imaju manju tendenciju širenja: 17% visoko-gradusnih i 3% nisko-gradusnih (8). Juvenilni pilocitični astrocitom ukoliko je lokalizovan u talamusu ili hipotalamusu može da daje leptomeningealnu diseminaciju. Ekstraneuralne metastaze predstavljaju neuobičajen način širenja tumora mozga koji se nešto češće nalazi kod meduloblastoma i tumora germinativnih ćelija. Najčešća mesta su: kost, kostna srž, pluća, jetra, limfni nodusi. Ovakva diseminacija može da bude i jatrogeno uzrokovana postavljanjem ventrikulo-peritonealnog (VP) šanta.

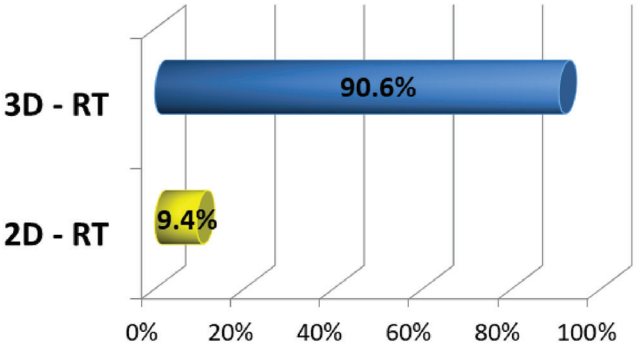
Većina tumora mozga, sem tumora germinativnih ćelija, prvenstveno se leči primenom hirurgije. Radioterapija je esencijalna komponenta tretmana za mnogu decu sa CNS tumorima. Starost deteta u vreme radioterapije mozga ima značajne reperkusije na razvoj kognitivnih funkcija zbog jonizujućim zračenjem izazvane inhibicije neurogeneze (9). Zbog visokog rizika od neurokognitivne toksičnosti zračenja u veoma mladom uzrastu, radioterapija se u većini slučajeva ne preporučije kod dece mlađe od 3 godine.

Za većinu tumora, definisanje ciljnih volumena najbolje se ostvaruje korišćenjem CT simulacije u koregistraciji sa CT-MR imidžingom. Obično se sprovodi lokalna radioterapija na postoperativno ležište tumora. Jedna od najzahtevnijih tehnika u radioterapiji, koja se vrlo često primenjuje kod dece, je tehnika kraniospinalne zračne terapije. Pri korišćenju ove tehnike cela neuralna osovina treba da bude uključena u ciljni volumen (čitav mozak i kičmena moždina kao i čitav subarahnoidalni prostor). Kraniospinalna radioterapija se klasično sprovodi iz 4 polja: dva opozitna lateralna za pokrivanje kranijuma i po jedno direktno na gornji i donji deo kičme. Pri korišćenju standardnih tehnika, donje granice bočnih polja čitavog mozga su usklađene sa kranijalnom granicom gornjeg kičmenog polja, obično sa pokretnim spojem između polja za kako bi se smanjio rizik od subdoziranja ili predoziranja na kičmenoj moždini. Za kaudalnu granicu polja, treba obratiti posebnu pažnju na završetak tekalne vreće. Položaj je uglavnom pronacioni uz korišćenje termoplastične maske za imobilizaciju. Opseg doza za kraniospinalno zračenje je 23.4-36Gy, a za lokalno zračenje 54-59.8Gy.

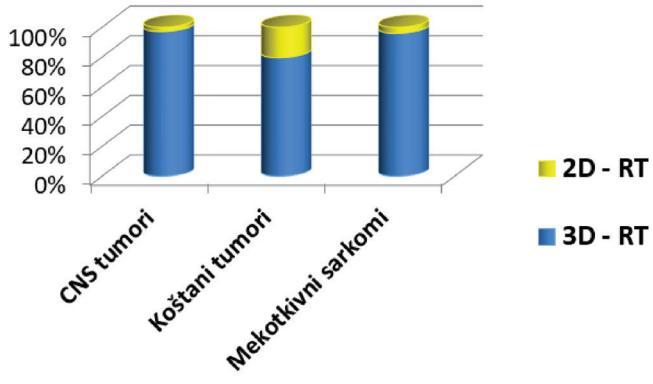
Zračenje celokupnog ventrikularnog sistema se najčešće koristi kod pacijenata sa CNS tumorima germinativnih ćelija (10). Zbog toga što je subependimalno širenje tumora često, ciljni volumen uključuje obe bočne, treću i četvrtu moždanu komoru sa adekvatnim marginama. Ako se prilikom zračenja koriste bočna opozitna polja u ovom slučaju očuvanje moždanog parenhima neće biti veliko. Bolja pošteda mozga se može postići korišćenjem konformalnijih tehnika radioterapije.

Nakon primene ovako opsežnih tehnika zračenja, preživeli su u značajnoj meri pod rizikom od razvoja dugoročnih sevela (neurološki deficiti, neurokognitivni i bihejvioralni efekti, endokrina disfunkcija, vaskulopatija i razvoj sekundarnih tumora).

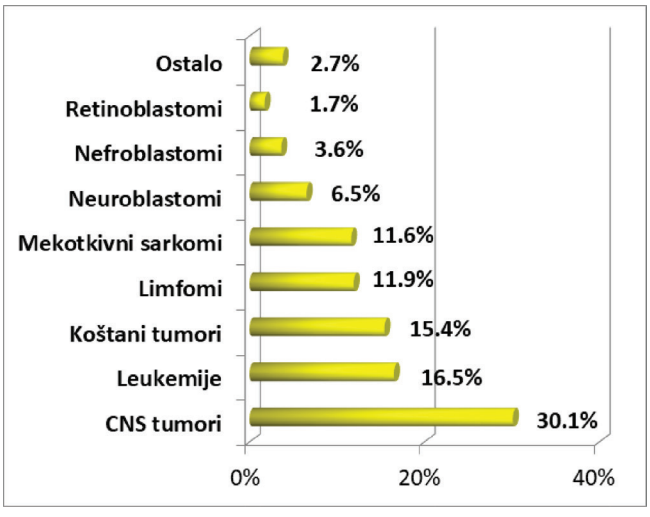
Grafikon 3. Distribucija dece prema primenjenoj tehnici radioterapije



Grafikon 4. Distribucija dece prema primenjenoj tehnici radioterapije u odnosu na različite osnovne dijagnoze



Grafikon 5. Distribucija dece prema različitoj osnovnoj dijagnozi



Leukemije

Akutna limfoblastna leukemija (ALL) predstavlja najčešći pedijatrijski malignitet (80%). U većini slučajeva (oko 90%) ovi bolesnici imaju dugogodišnje preživljavanje. Pacijenti se klasifikuju u grupe rizika na osnovu broja leukocita u vreme dijagnoze i citogenetskog profila na osnovu čega se određuje terapija.

Osnovni vid lečenja leukemija je hemioterapija. Uloga radioterapije je uglavnom u profilaktičkom ili terapijskom tretmanu kranijuma u kombinaciji sa sistemskom terapijom kod pacijenata sa ALL.

CNS profilaksa se može sprovesti putem iradijacije CNS-a, intratekalnom hemioterapijom i/ili visokodoznom sistemskom hemioterapijom. Cilj je predupreditи CNS bolest ili relaps uništavanjem leukemijskih ćelija na mestima koja nisu lako dostupna sistemskoj hemioterapiji zbog krvno-moždane barijere. Obzirom na značajne kasne sekvele (oštećenje neurokognitivnih funkcija, hipotalamopituitarna disfunkcija, sekundarni maligniteti), kao i na unapređenje sistemske terapije (agensi koji prolaze krvno-moždanu barijeru), kranijalna iradijacija se sve ređe upotrebljava u inicijalnoj terapiji ALL (11). Trenutno se kranijalna iradijacija koristi selektivno kod pacijenata sa visokim rizikom. Spinalni region se tretira intratekalnom hemioterapijom, pre nego radioterapijom.

Kranijalna radioterapija se sprovodi lateralnim opozitnim poljima. U ciljni volumen moraju da budu obuhvaćene kranijalni meningealni omotači koji se kaudalno protežu do C2 ili C3 pršljena. Posebnu pažnju treba obratiti na uključivanje kribriformne ploče, temporalnih lobusa i baze kranijuma u ciljni volumen (12). Kako bi se prevenirali okularni relapsi bolesti, posteriorne 1/3 orbita je potrebno uključiti u ciljni volumen, dok se očna sočiva moraju zaštiti, preporučuje se usperavanje pogleda pacijanta ka stopalima. Pacijenti se zrače u supinacionom položaju sa imobilizacionom termoplastičnom maskom. Najčešći dozni režimi su TD 12 Gy u 8 seansi za profilaktičko zračenje i TD 18 Gy u 12 seansi za terapijsko zračenje kranijuma.

Koštani tumori

Ewing-ov sarkom (ES) je drugi najčešći koštani tumor dečijeg uzrasta, posle osteosarkoma. Etiologija bolesti je nepoznata. ES može da se javi bilo gde u telu. Koštani tumori mogu da imaju intraosealnu i ekstraosealnu komponentu.

Patohistološki ES pripada familiji tumora malih, okruglih, plavih ćelija koje nastaju iz mezenhimalnih stem ćelija. 95% ima translokaciju između EWS gena na hromozomu 22 i FLI1 gena na hromozomu 11 ili ERG gena na hromozomu 21: t(11:22)(q24:q12) ili t(21:22)(q22:q12). U ESFT, postoji ekspresija proto-onkogrena c-myc (13).

Najčešća lokalizacija ES su donji ekstremiteti. ES se šire direktnom ekstenzijom primarnog tumora u okolno meko tkivo i koštane strukture. Oko 25% ima udaljene metastaze prilikom dijagnoze. One su najčešće hematogene i to u plućima i drugim, udaljenim kostima.Prognoza bolesti zavisi od veličine i lokalizacije primarnog tumora, kao i prisustva udaljenih metastaza. Lošija prognoza aksijalnih lezija je verovatno posledica činjenice da su ovi tumori znatno većih dimenzija prilikom dijagnoze u poređenju sa tumorima ekstremiteta.

Shodno preporukama, lečenje treba otpočeti indukcionom multiagensnom hemioterapijom u toku 6-12 nedelja pre lokalnog tretmana. Nakon indukcione hemioterapije, potrebna je reevaluacija bolesti (kako lokalizovane tako i metastatske). U slučaju povoljnog odgovora (kompletne ili parcijalne remisije), potrebno je sprovesti lokalno lečenje (hirurgija, radioterapija), a potom nastaviti sa hemioterapijom. U slučaju nepovoljnog odgovora, prognoza bolesti je loša i lečenje treba nastaviti lokalnom terapijom ili promeniti režim hemioterapije (14).

Pacijenti koji imaju manje parcijalnog odgovora na indukcionu hemioterapiju (manje od 50% smanjenja tumorske mekotkivne mase ili loš histološki odgovor na hirurškom preparatu) imaju malu šansu za izlečenje.

Radioterapija se može primeniti pre hirurgije radi smanjenja tumorske mase i postizanja veće šanse za radikalnu resekciju. Mane preoperativne radioterapije su veća učestalost postoperativnih infekcija i otežano zarastanje kosti. Kada se radioterapija primenjuje kao postoperativna omogućen je uvid u patohistološki odgovor tumora na indukcionu hemioterapiju, kao i uvid u resekcione margine. Pri ovom vidu zračne terapije, veći su zračni volumeni jer neophodno obuhvataju kompletan ožiljak. Radikalna/definitivna radioterapija je ranije bila standard. I dalje se primenjuje kao opcija za velike, neresektabilne tumore. Prednosti su što omogućava manje odlaganje hemioterapije zbog nepostojanja zarastanja operativne rane. Nažalost, povezana je sa manjom lokalnom kontrolom u odnosu na kombinovani pristup lokalnog lečenja (15).

U zavisnosti od lokalizacije bolesti, pacijenti se mogu tretirati u supinaciji, pronaciji ili lateralnoj poziciji. Koristi se CT simulacija, ali se preporučuje fuzija sa inicijalnim i posthemioterapijskim MR imidžingom (najbolje demarkiraja ceo tumor uključujući intra- i ekstraosealnu komponentu). Kod tumora koji su uz torakalnu ili peritonealnu duplju, ciljni volumeni se definišu o odnosu na marginu tumora nakon indukcione hemioterapije kada se zdravi odgani vraćaju u normalnu anatomsku lokalizaciju te nema potrebe za zračenjem tih zdravih

tkiva. Preporučene radioterapijske doze su u opsegu 45-55.8Gy uz dozu po frakciji 1.8Gy.

Skelet dece i adolescenata je osetljiv na zračenje i moguće su brojne sekvele: deprivacija rasta dugih kostiju, frakture dugih kostiju, hipoplazija pljosnatih kostiju, skolioza, mišićna hipoplazija, limfedem, indukovani sarkomi. Zbog moguće skolioze, prilikom zračenja pršljenskih tela, pravilo je da celo pršljensko telo mora biti u ciljnom volumenu (16).

Mekotkivni sarkomi

Rabdomiosarkom (RMS) je najčešći mekotkivni sarkom dece i adolescenata. Nastaje iz nezrelog poprečno-prugastog mišićnog tkiva i zajedno sa ES, neuroblastomom i limfomom spada u dečije tumore tzv. malih plavih okruglih ćelija. Patohistološki RMS se deli na: embrionalni, alveolarni i pleomorfni tip.

Multiagensna hemioterapija se primenjuje u tretmanu svih pacijenata sa rabdomiosarkomom (17). Hirurško lečenje je važna komponenta lokalnog tretmana RMS. Cilj hirurškog lečenja je kompletna resekcija tumora. U pedijatrijskoj populaciji, primarni cilj je takođe prezervacija organa.

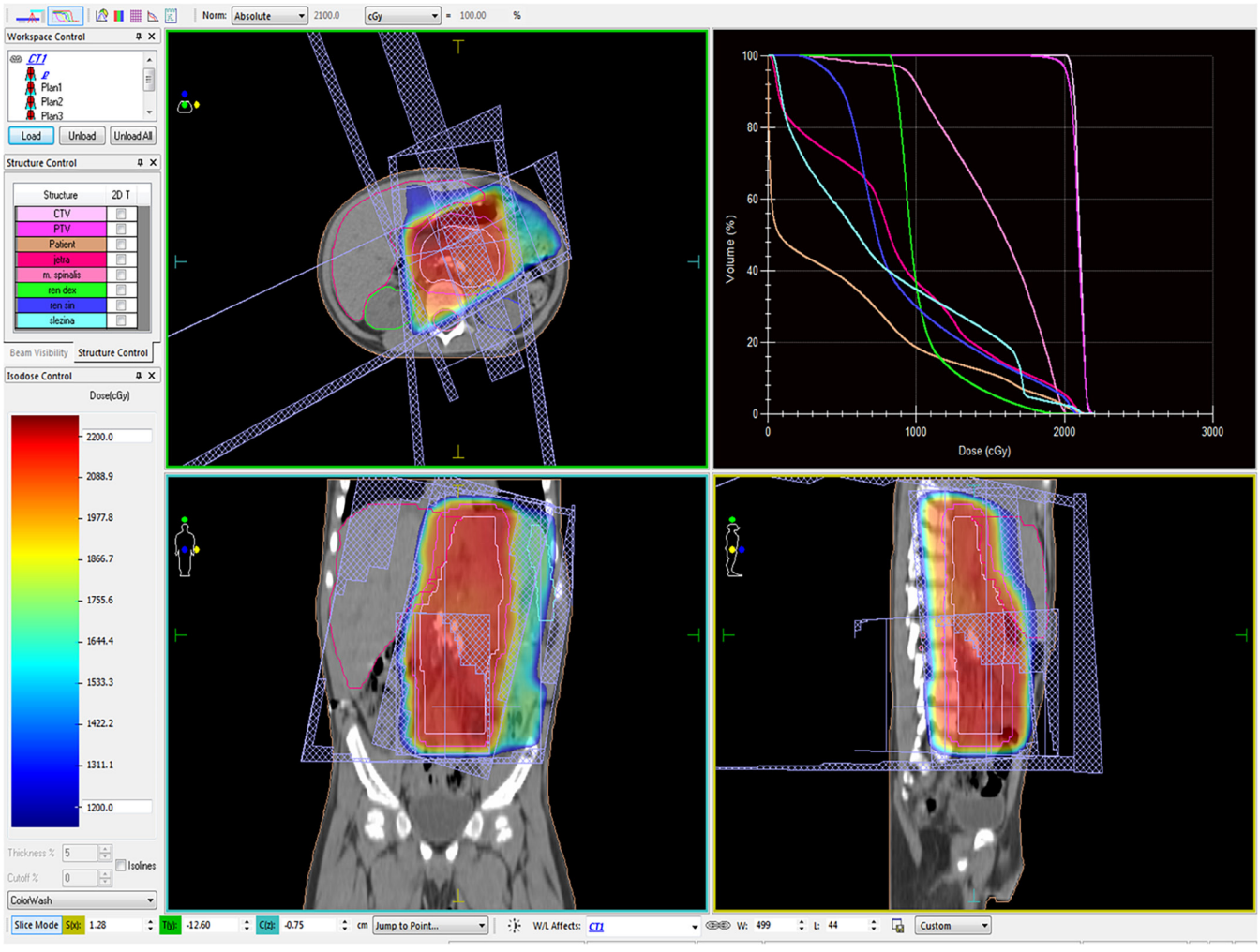
Doze i vreme primene radioterapije zavise od kliničke grupe i lokalizacije bolesti (18). Prema preporukama, svi pacijenti sem kompletno resekovanog embrionalnog RMS se tretiraju radioterapijom. Pacijenti sa mikroskopskom rezidualnom bolešću se tretiraju dozom 41,4 Gy, dnevnom dozom 1,8 Gy. Orbitalni tumori se obično tretiraju dozom od 45 Gy. U regiji glave i vrata, gde najčešće postoji makroskopska rezidualna bolest koju treba tretirati radioterapijom, potrebna je doza od 50,4 Gy.

Neuroblastom

Neuroblastom (NB) je najčešći ekstrakranijalni solidni tumor kod dece. Skoro 90% pacijenata je mladja od 5 godina (19). NB može da se javi bilo gde u telu. Najčešća lokalizacija tumora je abdomen, mada često može imati ishodište u paraspinalnom simpatičkom lancu u vratu, grudima i pelvisu.

NB zajedno sa ganglioneuromom i ganglioneuroblastomom pripada neuroblastnoj grupi tumora koji su na različitom stupnju diferencijacije. Neuroblastom pripada familiji tumora malih, okruglih, plavih ćelija i tipično je imunohistohemijski pozitivan na neuronalne markere kao što su sinaptofizin i neuron-specifična enolaza. Patohistološka slika je važan prognostički faktor.

Slika 1. Primer 3D konformalne radioetrapije neuroblastoma sprovedene u IORS



U najvećem broju slučajeva, bolest se manifestuje kao metastatska (20). Što je dete starije životne dobi, tendencija je da bolest bude više diseminovana pri prezentaciji. Bolest može da metastazira limfogeno i hematogeno a najčešća mesta sekundarnih depozita su kostna srž, kost, jetra, limfni čvorovi i koža. Metastaze u mozgu i plućima nisu česte.

Prognostički faktori su: starost deteta, posthirurški stadijum, histološka grupa, DNK ploidija. U jednoj grupi NB onkogen MYCN koji je lociran na 2p24 može da bude amplifikovan, što je snažno povezano sa lošom prognozom.

Na osnovu navedenih kriterijuma, bolest se prema INRG klasifikacionom sistemu deli na: nisko-, srednje- i visoko rizičnu grupu (21).

Tretman NB (hirurgija, hemioterapija, radioterapija) se individualno određuje na osnovu parametara bolesti i pripadnosti određenoj grupu rizika. Zbog tendencije bolesti ka sistemskom širenju, hemioterapija predstavlja osnov terapije. Hirurgija nije indikovana u povoljnoj histološkoj grupi i kliničkoj grupi niskog rizika. U grupi visokog rizika, indikovana je maksimalna bezbedna tumorska resekcija. Radioterapija se više ne preporučuje u nisko i srednje rizičnoj grupi. U grupi visokog rizika, ima značajnu ulogu u multidisciplinarnom lečenju.

Tehnika radioterapije zavisi od lokalizacije tumora. Ciljni volumen za abdominalnu lokalizaciju obuhvata: volumen tumora nakon indukcione HT i regionalne zahvaćene paraaortne limfne noduse. Za većinu pacijenata optimalna je konvencionalna tehnika opozitnim poljima. Ukoliko postoji blizak odnos sa nekom kritičnom strukturom, preporučuje se neka konformalnija tehnika. Ležište primarnog tumora predstavlja najrizičnije mesto za relaps i nakon agresivne hemioterapije. Efikasna doza na ležište primarnog tumora je 20-24Gy. Hirurgija i radioterapija omogućavaju maksimalnu lokalnu kontrolu kod visokorizične grupe pacijenata, i time popravljaju prognozu bolesti (22).

Nefroblastom

Vilmsov tumor ili nefroblastom, je najčešći abdominalni tumor kod dece i čini 5-6% svih dečijih kancera.

Najvažniji prognostički faktor za nefroblastom je patohistološki podtip, sa najgorom prognozom kod anaplastičnog oblika a najboljom kod povoljne histologije.

U Severnoj Americi se najpre radi nefrektomija a potom sprovodi hemioterapija i eventualno zračna terapija prema protokolima (23). U Evropi se hemioterapija primenjuje pre nefrektomije. Biopsija renalne mase se ne preporučuje jer oštećenje renalne kapsule znači veći stadijum i potrebu za zračnom terapijom.

Radioterapija abdomena se primenjuje dve nedelje nakon nefrektomije. Kod nefroblastoma povoljne histologije, radioterapija se primenjuje u stadijumu III lokalne bolesti, tj. ako postoje pozitivni limfni nodusi i pozitivna mikroskopska ivica resekcije. Ciljni volumen uključuje primarno ležište (tumora i bubrega) i pridružene paraaortne limfne noduse. U zračno polje treba uključiti pršljenska tela celom širinom kako ne bi došlo do skolioze. Ukoliko je postojala preoperativna ruptura tumora, u slučaju peritonealnih metastaza ili operativnog difuznog rasipanja tumora, potrebna je zračna terapija celog abdomena. U nekim slučajevima plućnim metastaza, primenjuje se i zračna terapija celih pluća.

U stadijumima I-IV fokalnog anaplastičnog tumora i stadijumu I-II difuznog anaplastičnog tumora, RT doze i polja su identični sa nefroblastomom povoljne histologije (24). Stadijum III difuzni anaplastični treba da primi veću dozu.

Zbog odličnog preživljavanja dece sa nefroblastomom, cilj terapije mora da uključi i minimiziranje kasnih neželjenih efekata radioterapije (25). Neke od najčešćih sekvela su: skolioza, kifoza, hipoplazija mekog tkiva, moguće su i renalna disfunkcija, opstrukcija creva, srčana oboljenja, sekundarni maligniteti.

Iskustvo IORS u pedijatrijskoj radioterapiji

Godišnje se zračnom terapijom u Institutu za onkologiju i radiologiju Srbije leči 60 do 80 pacijenata uzrasta od 1 do 18 godina. Za decu uzrasta do 3 godine, izuzetno retko i stariju, zračna terapija se sprovodi u anesteziji što ističemo kao značajno iskustvo i kvalitet rada naše ustanove.

U desetogodišnjem periodu u našoj ustanovi, od januara 2007. do septembra 2016.godine, radioterapijom je lečeno 648 dece, od kojih 59 uzrasta manjeg od 3 godine (Grafikon 1). Radioterapijskom tretmanu je podvrgnuto nešto više dečaka u odnosu na devojčice (Grafikon 2). Kod najvećeg broja dece, 90.6%, sprovodena je zračna terapija upotrebom 3D konfomalne tehnike (3D-CRT), a kod malog broja, 9.4% konvencionalnom radioterapijom (2D-RT) (Grafikon 3). Gotovo sva deca sa tumorima CNS i sarkomima mekih tkiva tretirana su pomoću 3D-CRT, kao i nešto manji procenat pacijenata sa koštanim tumorima i hematološkim malignitetima (Grafikon 4). Najčešći pacijenti bili su deca sa tumorima centralnog nervnog sistema 30.1%, leukemijom 16.5%, koštanim tumorima 15.4%, limfomima 11.9%, mekotkivnim sarkomima 11.6%, neuroblastomom 6.5%, nefroblastomom 3.6%, retinoblastomom 1.7% i ostalim retkim tumorima (Grafikon 5). Uz operativno lečenje najveći broj dece lečen je hemioterapijom i radioterapijom, 89.8%. Većina dece kod kojih je sprovedena radioterapija lečena je hemioterapijom u našoj ustanovi, 45.8%. Kod malog broja dece sprovedena je radioterapija kao jedini terapijski pristup, 10.2%.

Upotreba 3D-CRT je u Institutu za onkologiju i radiologiju Srbije tokom godina beležila stalni porast, da bi konačno postala standard pri radioterapjskom tretmanu dece. Zadovoljni smo implementacijom 3D-konformalne radioterapije u našoj ustanovi (Slika1).

Zaključak

U Institutu za onkologiju i radiologiju Srbije, kao centralnoj ustanovi za pedijatrijsku radioterapiju, u potpunosti je usvojena 3D-CRT kao standard u lečenju dece i omladine. U proteklom desetogodišnjem periodu stekli smo sopstvena iskustva koja će nam biti od velike koristi prilikom uvođenja naprednijih tehnika koje očekujemo daljom kupovinom uređaja i opreme za radioterapiju.

Napomena

Rad je usmeno izložen na mini simpozijumu "Savremeni principi pedijatrijske onkologije", na 46. simpozijumu Stremljenja i novine u medicini, Medicinski fakultet u Beogradu, 13.12.2017.godine.

LITERATURA

1. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. J Natl Cancer Inst 2009;101(13):946–958.
2. Guerin, S., C.Guibout, A.Shamsaldin, et al. Concomitant chemo-radiotherapy and local dose of radiation as risk factors for second malignant neoplasms after solid cancer in childhood: A case-control study. International Journal of Cancer 2007;120 (1):96–102.
3. D'Souza, W.D., and I.I.Rosen. Nontumor integral dose variation in conventional radiotherapy treatment planning. Medical Physics 2003;30 (8):2065–71
4. Aoyama, H., D.C.Westerly, T.R.Mackie, et al. Integral radiation dose to normal structures with conformal external beam radiation. International Journal of Radiation Oncology Biology Physics 2006; 64 (3):962–7.
5. Allan, J.M., and L.B.Travis. Mechanisms of therapy-related carcinogenesis. Nature Reviews Cancer 2005;5 (12):943–55.
6. Ward E, DeSantis C, Robbins A, et al. Childhood and adolescent cancer statistics. CA Cancer J Clin. 2014;64:83–103
7. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 2006;24(25):4202–4208.
8. Beltran C, Naik M, Merchant TE. Dosimetric effect of setup motion and target volume margin reduction in pediatric ependymoma. Radiother Oncol 2010;96(2):216–222.
9. Ellenberg, L., Q.Liu, G.Gioia, et al. Neurocognitive status in long-term survivors of childhood CNS malignancies: A report from the Childhood Cancer Survivor Study.Neuropsychology 2009;23 (6):705–17.
10. Khatua, S., G.Dhall, S.O'Neil, et al. Treatment of primary CNS germinomatous germ cell tumors with chemotherapy prior to reduced dose whole ventricular and local boost irradiation.Pediatric Blood and Cancer 2010;55 (1):42–6.
11. Edelstein, K., N.D'Agostino, L.J.Bernstein, et al.Long-term neurocognitive outcomes in young adult survivors of childhood acute lymphoblastic leukemia.Journal of Pediatric Hematology/Oncology 2011;33 (6):450–8.
12. Silber, J.H., J.Radcliffe, V.Peckham, et al. Whole-brain irradiation and decline in intelligence: The influence of dose and age on IQ score. Journal of Clinical Oncology 1992;10 (9):1390–6.
13. Bailly RA, Bosselut R, Zucman J, et al. DNA-binding and transcriptional activation properties of the EWS-FLI-1 fusion protein resulting from the t(11;22) translocation in Ewing sarcoma. Mol Cell Biol. 1994;14:3230–3241.
14. Shamberger RC, LaQuaglia MP, Gebhardt MC, et al. Ewing sarcoma/primitive neuroectodermal tumor of the chest wall: impact of initial versus delayed resection on tumor margins, survival, and use of radiation therapy. Ann Surg. 2003;238:563–567
15. Donaldson, S.S. Ewing sarcoma: Radiation dose and target volume.Pediatric Blood & Cancer 2004; 42 (5):471–6.
16. Ginsberg, J.P., P.Goodman, W.Leisenring, et al. Long-term survivors of childhood Ewing sarcoma: Report from the childhood cancer survivor study. Journal of the National Cancer Institute 2010;102 (16):1272–83.
17. Stevens MC, Rey A, Bouvet N, et al. Treatment of nonmetastatic rhabdomyosarcoma in childhood and adolescence: third study of the International Society of Paediatric Oncology—SIOP Malignant Mesenchymal Tumor 89. J Clin Oncol. 2005;23(12):2618–2628.
18. Terezakis S, Wharam. Radiotherapy for rhabdomyosarcoma: indications and outcome. Clin Oncol 2013 Jan;25(1):27-35.
19. Woods WG, Gao RN, Shuster JJ, et al. Screening of infants and mortality due to neuroblastoma. N Eng J Med. 2002;346:1041–1046.
20. Mullassery D, Farrelly P, Losty PD. Does aggressive surgical resection improve survival in advanced stage 3 and 4 neuroblastoma? A systematic review and meta-analysis. Pediatr Hematol Oncol. 2014;31:703–716
21. Cohn SL, Pearson AD, London WB, et al. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. J Clin Oncol. 2009;27:289–297.
22. Zage PE, Kletzel M, Murray K, et al. Outcomes of the POG 9340/9341/9342 trials for children with high-risk neuroblastoma: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2008;51:747–753.
23. Neville HL, Ritchey ML. Wilms' tumor: overview of National Wilms' Tumor Study Group results. Urol Clin North Am. 2000;27:435–442.
24. Dome JS, Cotton CA, Perlman EJ, et al. Treatment of anaplastic histology Wilms tumor: results from the fifth National Wilms Tumor Study. J Clin Oncol. 2006;24:2352–2358
25. Cotton CA, Peterson S, Norkool PA, et al. Early and late mortality after diagnosis of Wilms tumor. J Clin Oncol. 2009;27:1304–1309.

Institut za epidemiologiju, Medicinski fakultet, Univerzitet u Beogradu, Beograd, Srbija

AUTISM AND MMR VACCINE

AUTIZAM I MMR VAKCINA

Nataša Maksimović, Darija Kisić Tepavčević

Summary

Autism is a complex neurological developmental disorder with wide range of symptoms. Among them, poor social interaction, limited and repeated behavioral patterns are the most important for diagnosing the disorder. The prevalence of autism is rising constantly. One of the theories drawing the greatest public attention for a long time is a possible association between MMR vaccine and risk of autism. The first study aimed to investigate this association is the one conducted in 1998. As the results supported the theory that MMR vaccine increased the risk of autism, MMR immunization coverage decreased dramatically which further led to measles outbreaks, even in those countries where the disease was almost eradicated. Soon after that publication, new studies denying any association between MMR vaccine and risk of autism were published. Among them, systematic review published in 2012, including 57 epidemiological studies with 14.700.000 children is particularly important. Although the etiology of autism is not completely clarified, there are strong evidence on the presence of neurobiological changes with significant genetic component underlying the etiology. According to recent literature data, morphological changes in brain of children age 6 to 12 months, that is, before the administration of MMR vaccine, precede clinical symptoms of autism.

Key words: MMR, autism, prevalence, etiology, epidemiological studies

Sažetak

Autizam je kompleksan neurološki razvojni poremećaj sa širokim spektrom simptoma, među kojima se izdvajaju slaba ili nikakva socijalna interakcija i komunikacija i ograničeni i ponavljajući obrasci ponašanja, kao najznačajniji simptomi za postavljanje dijagnoze. Prevalencija autizma je u stalnom porastu. Jedna od teorija koja već dugi niz godina budi pažnju javnosti je i teorija o mogućoj vezi između MMR vakcine i rizika za nastanak autizma. Prva studija koja je imala za cilj da ispita ovu povezanost, izvedena je još davne 1998. godine. Kako su rezultati ove studije govorili u prilog teorije da MMR vakcina povećava rizik za nastanak autizma, došlo je do pada obuhvata vakcinacije MMR vakcinom i do masovne pojave malih boginja i u onim zemljama gde su bile gotovo eliminisane. Ubrzo su usledile brojne studije koje su opovrgle svaku povezanost između MMR vakcine i rizika za nastanak autizma, među kojima je i sistematski pregled literature iz 2012. godine, koji je uključio 57 epidemioloških studija, sa 14.700.000 dece. I ako etiologija autizma nije sasvim razjašnjena, postoje snažni dokazi o prisustvu neurobiološke osnove sa značajnom genetskom komponentom kod obolelih. Prema najnovijim leteraturnim podacima, morfološke promene mozga u uzrastu 6-12 meseci, dakle, pre dobijanja MMR vakcine, prethode kliničkom ispoljavanju autizma.

Ključne reči: MMR, autizam, prevalencija, etiologija, epidemiološke studije

Autizam – definicija i dijagnoza

Autizam je kompleksan neurološki razvojni poremećaj sa širokim spektrom simptoma, među kojima se izdvajaju slaba ili nikakva socijalna interakcija i komunikacija i ograničeni i ponavljajući obrasci ponašanja, kao najznačajniji simptomi za postavljanje dijagnoze (1). Autizam, zajedno sa pervazivni razvojnim poremećajem (PRP), nespecifičnim PRP i Aspergerovim sindromom (AS) čini spektar autističnih poremećaja (SAP) (2). Rana dijagnoza autizma je izuzetno važna jer omogućava pravovremeno uključivanje u posebne i specijalizovane programe, za koje je pokazano da značajno poboljšavaju komunikaciju i socijalnu interakciju (3). Kriterijumi za uključivanje u navedene programe često su ograničeni samo na onu decu koja imaju postavljenu dijagnozu SAP, što ukazuje na značaj ranog otkrivanja. S druge strane, teškoće koje mogu da se jave pri postavljanju dijagnoze autizma, kao i diferencijalno dijagnostički problemi kod najmlađih, često otežavaju rano otkrivaje autizma (4).

Dijagnoza SAP u najranijem uzrastu je moguća, ali je klinički teško izvodljiva zbog preklapanja sa značajnim i ozbiljnim govornim i opštim razvojnim poremećajima koji nastaju zbog mentalne retardacije (3, 5). *Van Daalen* i saradnici su 2009. godine objavili da čak i iskusni kliničari imaju nesuglasice kada je u pitanju diferencijalna dijagnoza SAP i mentalna nesposobnost bez poremećaja iz SAP kod dece uzrasta 2 godine (6), dok je *Lord* pokazao da su dijagnostičke razlike izraženije već u uzrastu od 3 godine (3, 5).

Prevalencija autizima

Leo Kanner je 1943. godine započeo seriju slučajeva dece sa autizmom, tvrdnjom da mu je ovo stanje prvi put privuklo pažnju 1938. godine (7).

Prve studije o prevalenciji autizma sprovedene su tokom 60-ih i 70-ih godina prošlog veka u SAD-u i u Velikoj Britaniji. Procenjena prevalencija autizma iznosila je 2 do 4 na 10.000 dece (8, 9, 10). Ovakvi rezultati odavali su utisak da je autizam redak poremećaj. Takođe, prve studije prevalencije autizma ukazale su i na jasnu razliku između polova, pri čemu su dečaci čak 4 puta češće

obolevali u odnosu na devojčice. Kada su ustanovljeni dijagnosički kriterijumi autizma krajem 80-ih i početkom 90-ih godina XX veka, prevalencija autizma u svetu pokazala je dramatičan porast (11, 12, 13).

Rezultati prospektivne kohortne studije koja je za cilj imala procenu prevalencije SAP u populaciji dece iz Velike Britanije, pokazala je da u njihovom reprezentativnom uzorku prevalencija iznosi 30,8 na 10.000 dece (14). Navedena prevalencija bila je slična prevalenciji koju su u svojoj studiji prijavili *Bertrand* i saradnici 2001. godine, a koja je iznosila 40,5 na 10.000 dece (15). U studiji koju su u Velikoj Britaniji 2009. godine sproveli *Baron-Cohen* i saradnici, pokazano je da je prevalencija autizma 94 na 10.000 dece, ukoliko se podaci o deci preuzimaju iz Nacionalnog registra, dok je prevalencija dobijena na osnovu skrininga i kliničke dijagnoze među decom uzrasta 5–9 godina nešto viša i iznosi 99 na 10.000 dece (16).

Počev od 2000. godine, CDC sprovodi aktivni nadzor nad SAP među osmogodišnjom decom u određenim centrima u SAD, na svake 2 godine (17). Prema procenama CDC-ja, prevalencija u SAD-u je 2000. godine iznosila 6,7 na 1000 dece, a njena vrednost je do 2010. godine porasla dvostruko više, na 14,7 na 1000 dece (1,5%) (18-20). Iako autizam može biti dijagnostikovan već u usrastu od 2 godine, u SAD-u je medijana uzrasta 5,2 – 5,7 godina (21, 22). Prema podacima CDC-ja, kod većine dece u SAD-u procena psihomotornog razvoja se obavlja do uzrasta od 8 godina. Iz ovog razloga, CDC analizira prevalenciju autizma u uzrastu od 8 godina, a potom na svake dve godine, jer je to najefikasniji način da se sagleda da li postoje promene u vremenskom trendu prevalencije (23).

Jedna od prvih epidemioloških studija koja je sprovedena na teritoriji Meksika pokazala je da je prevalencija dece sa SAP 0,87%, što je u saglasnosti sa prethodno objavljenim pregledima literature iz 2009. godine, prema kojima se prevalencija kretala 0,6–1% (11, 24-26). Prevalencija u Latinskoj Americi je nešto niža. U Venecueli je 2008. godine iznosla 0,17% za sve poremećaje iz SAP, i to 0,11% za autistični poremećaj, i 0,06% za Aspergerov sindrom, u populaciji dece uzrasta 3 – 9 godina (27).

Prema rezultatima studije sprovedene u Južnoj Koreji 2015. godine, prevalencija autizma je nešto viša i iznosi 2,64% kod dece uzrasta 7–12 godina. Ovi rezultati su upadljivi ne samo zbog činjenice da je procenjena prevalencija viša u odnosu na onu koju su 2012. godine dobili *Elsabaggh* i sar (19-25), već i zbog toga što je 90% dece sa autizmom išlo u redovnu školu, dok 72% njih nije imalo nikakav psihijatrijski poremećaj u ličnoj anamnezi (28).

Statistički podaci koji se odnose na prevalenciju autizma u odabranim zemljama sveta za 2017. godinu pokazuju da je prevalencija autizma najviša u Japanu i iznosi 161 na 10.000 dece. Na drugom mestu je Velika Britanija u kojoj je prevalencija autizma 94 na 10.000 dece, dok u Švedskoj iznosi 72 na 10.000 dece. Sa druge strane, Brazil, Hong Kong i Portugalija prijavljuju najniže vrednosti prevalencije, koje iznose 27, 17 i 9,2 na 10.000 dece (29).

Postavlja se pitanje koji su razlozi za porast prevalencije autizma. Dijagnoza autizma se sve češće postavlja počev od 1979. godine, a istraživanja koja su sprovedena objašnjavaju oko 50% porasta prevalencije autizma. Jedan od mogućih razloga za porast prevalencije autizma je promena dijagnostičkih kriterijuma tokom vremena. Godine 1952. autizam je definisan kao „šizofrenija sa ranim početkom". Tokom 1980. godine dobija novi naziv – „infantilni autizam", a 1987. godine ponovo menja naziv u „autistični poremećaj". Tokom prethodne decenije, uobičajeni naziv autizam pokriva čitav spektar bihejvioralnih, komunikacijskih i socijalnih poremećaja koji se jednim imenom nazivaju SAP, a koji uključuje autistični poremećaj, Aspergerov sindrom i ostale srodne poremećaje. Dijagnoza autizma je prilično subjektivna. Socijalne veštine osoba sa autizmom se razlikuju u mnogome u odnosu na opštu populaciju, kao i ostali oblici ponašanja koji su u sprezi sa autizmom. Postavlja se pitanje u kom trenutku odsustvo spontanosti i nemogućnost uspostavljanja kontakta očima predstavljaju medicinski problem. Drugim rečima, učestalost dijagnoze predstavlja odraz mogućnosti roditelja da prihvate dijagnozu. Na ovaj način može da se objasni jedan deo porasta prevalencije autizma (29). Prema *Grinker*-u dijagnoza je promenljiva i predstavlja okvir koji funkcioniše u određenom zdravstvenom i socijalnom sistemu, a menja se zajedno sa promenama u društvu. Ovakve tvrdnje su pomogle da se objasni porast prevalencije autizma, što je *Grinker* pokazao u studiji sprovednoj u Južnoj Koreji (30).

Peter Bearman, sociolog sa Univerziteta Kolumbija, pokušao je da poveže detaljne dijagnostičke podatke kako bi sagledao širu sliku demografskih karakteristika i lične istorije osoba sa autizmom, što je dalje dovelo do sagledavanja socijalnih faktora koji utiču na dijagnozu. Takođe, prema *Bearman*-u, oko 50% zapaženog porasta prevalencije autizma može biti objašnjeno. Oko 25% porasta prevalencije autizma tokom prethodne dve decenije *Bearman* je pripisao tzv. „dijagnostičkom nagomilavanju", tj. promeni dijagnostičkih kriterijuma koji idu u korist SAP. Analizom zdravstvenih kartona dece sa autizmom, zaključio je da ono što je u jednom trenutku dijagnostikovano kao mentalna retardacija, zapravo predstavlja autizam (31). Oko 15% porasta prevalencije autizma može da se objasni povećanjem svesti o autizmu – sve više roditelja i pedijatara je upoznato sa ovim poremećajem (32). Prema *Bearman*-u, geografsko grupisanje objašnjava negde oko 4% povećanja prevalencije autizma. Najznačajniji klaster nalazi se u okolini Holivuda. Deca koja žive na teritoriji od 900 km^2 u okolini zapadnog Holivuda imaju 4 puta veći rizik za autizam

ili poremećaj iz ovog spektra u odnosu na decu koja žive u nekom drugom delu Kalifornije (32). Oko 10% povećanja prevalencije autizma može biti objašnjeno socijalnim promenama koje su, sa druge strane, uslovljene biološkim promenama: roditelji dobijaju decu u starijem uzrastu. Neka istraživanja su pokazala da deca čiji roditelji imaju više od 35 godina imaju veći rizik za razvoj autizma. Studije se dele na one koje su pokazale da godište majke ima značajan uticaj, kao i one koje su pokazale da je značajno godište oca, ali *Bearman*-ove studije koje su uključile roditelje starije od 40 godina pokazale su da je godište majke značajnije (33). Međutim, činjenica da 46% povećanja prevalencije ne može da se objasni ne znači da ovo povećanje predstavlja posledicu nekih novih zagađivača spoljašnje sredine (29).

Autizam i MMR vakcina

Veza između autizma i MMR vakcine učinila se prihvatljivom zato što se vakcinacija protiv malih boginja obavlja u drugoj godini života, a u to vreme, obično do uzrasta od 24 meseca, mogu da se zapaze prvi znaci autizma, bilo kao zastoj u razvoju ili kao gubitak već stečenih sposobnosti (regresija). Međutim, vremenska podudarnost ne znači da postoji uzročno-posledični odnos. Protiv uloge vakcinacije u nastanku autizma govori podatak da je učestalost ovog poremećaja nastavila da raste i u vreme kada je obuhvat vakcinacijom znatno opao širom sveta.

Godine 1998. dr *Andrew Wakefield,* britanski gastroenterolog, je u časopisu Lancet prikazao seriju slučajeva od 12 dece koja su se javila na odeljenje pedijatrijske gastroenterologije. U ličnoj anamnezi navedeno je da su deca imala normalan psihomotorni razvoj, ali su u jednom trenutku počela da gube prethodno stečene veštine (govor), uz dijareju i abdominalne bolove, a kod 9 njih postavljena je dijagnoza autizma. Deci su urađene sve gastroenterološke, neurološke i razvojne procene, kao i provera zdravstvenog kartona. Prema podacima koje su dali roditelji, simptomi kod dece poklapali su se sa vakcinacijom MMR vakcinom kod 8 od 12 dece, sa infekcijom virusom morbila kod jednog deteta, i zapaljenjem srednjeg uha kod ostalih. Dr *Wakefield* je u zaključku izneo moguću povezanost sa vakcinacijom MMR vakcinom, navodeći da je u seriji slučajeva koju je istraživao većina dece pokazala prve simptome autizma nakon vakcinacije (34). Uprkos maloj veličini uzorka, nedovoljno kontrolisanom dizajnu studije, kao i spekulišućoj prirodi zaključaka, rad je privukao veliku pažnju, a obuhvat MMR vakcinacijom je značajno opao, jer su roditelji bili zabrinuti rizikom za nastanak autizma nakon vakcinacije, pa je u nizu zemalja u kojima su male boginje bile već eliminisane došlo do njihove masovne pojave. (35).

Ubrzo počinju da se sprovode epidemiološke studije koje negiraju hipotezu o povezanosti između MMR vakcine i rizika za nastanak autizma (36, 37). Veza između MMR vakcine i rizika od nastanka autizma je sporna i zbog činjenice da je temporalna povezanost gotovo predodređena: oba događaja (MMR vakcinacija i autizam) dešavaju se u ranom detinjstvu (38). Prema navodima, „kauzalna povezanost između MMR vakcine i autizma nije pokazana jer su podaci nedovoljni“ (39). Takođe, *Lancet* se nakon toga izjasnio da je tokom istraživanja bilo sukoba interesa. Međutim, *Wakefield* i kolege su oslobođeni optužbe za kršenje etičkog kodeksa i naučno nepoštenje (40). Lancet je potpuno povukao rad u februaru 2010. godine, priznajući da nekoliko elemenata u radu nije bilo zadovoljavajuće, kao i da su oni u suprotnosti sa nalazima prethodnih istraživanja (41).

Od studije dr *Wakefield*-a do danas, preko 40 epidemioloških studija različitog dizajna prikazalo je da ne postoji povezanost između MMR vakcine i rizika za nastanak autizma.

Već 1999. godine *Taylor* i saradnici sprovode retrospektivnu analizu podataka o deci sa autizmom, koristeći kohortne dobne krive, kako bi pokazali da li vakcinacija MMR vakcinom zaista nosi rizik od nastanka autizma, kao i da li vreme vakcinacije utiče na pojavu simptoma. Pokazano je da uzrast u vreme dijagnoze ne zavisi od uzrasta u kome je data MMR vakcina, tj. da li je vakcina aplikovana pre ili posle usrasta od 18 meseci, a ni jedna od analiza nije ukazala na povezanost između MMR vakcine i autizma. Analiza serije slučajeva pokazala je da nema vremenskog grupisanja između MMR vakcine i dijagnoze autizma (36).

Do sličnih rezultata došla je i studija koja je ispitivala vremenske trendove autizma i vakcinacije MMR vakcinom u Kaliforniji. *Dales* i saradnici su zaključili da odsustvo povezanosti između temporalnih trendova MMR vakcinacije i broja SAP zapravo ne podržava hipotezu da je povećan obuhvat imunizacijom kod male dece povezan sa upadljivim rastućim sekularnim trendom SAP u Kaliforniji. Autori su istakli činjenicu da je obuhvat imunizacijom MMR vakcinom porastao u periodu od 1980. do 1994. godine, ali navedeni porast nije bio praćen porastom autizma, što je pokazala analiza kohortnih dobnih kriva (37).

Analiza vremenskih trendova u Velikoj Britaniji, koja je obuhvatila podatke iz medicinske dokumentacije lekara opšte prakse, kao i decu uzrasta do 12 godina koja su u periodu od 1988. do 1993. godine ispoljila simptome poremećaja iz autističnog spektra, pokazala je da je incidencija autizma kod dece uzrasta 2 do 5 godina značajno porasla u navedenom periodu, ali samo u datoj kohorti, dok je obuhvat imunizacijom bio viši od 95% za sve kohortne dobne grupe, tako da rezultati date studije nisu išli u prilog povezanosti između MMR vakcine i rizika za nastanak autizma. Dakle, ne postoji vremenska korelacija između obuhvata imunizacijom i incidencije

autizma u svakoj analiziranoj kohortnoj dobnoj grupi u navedenom periodu. Autori su porast incidencije autizma koji je pokazan analizom zdravstvene dokumentacije dece objasnili delimičnimm porastom svesti o ovom poremećaju koji je zapažen ne samo kod zdravstvenih radnika, već i kod roditelja, ali i promenama dijagnostičkih kriterijuma, pa čak i mogućim sredinskim faktorima koji još uvek nisu identifikovani. Svakako, studija je obezbedila dokaze koji ne podržavaju hipotezu postavljenu 1998. godine (42).

Retrospektivna kohortna studija iz 2002. godine, koju su sproveli *Madsen* i saradnici u Danskoj, obuhvatila je reprezentativni uzorak od preko 500.000 dece rođene između 1991. i 1998. godine. Istraživanje je pokazalo da je u uzorku bilo vakcinisano više od 80% dece. Relativni rizik za nastanak autizma u grupi vakcinisane dece iznosio je 0,92, dok je kod nevakcinisanih iznosio 0,83. Takođe, povezanost između uzrasta u vreme dobijanja vakcine i autizma nije pronađena ni u ovoj studiji. Data studija je zapravo obezbedila tri snažna dokaza koja idu protiv hipoteze da je MMR vakcina povezana sa rizikom od nastanka autizma. Prvo, rizik od autizma je sličan i kod vakcinisane i kod nevakcinisane dece, i kada se analiza radi u ukupnom uzorku, ali i kada se radi uzrasno-specifična analiza. Drugo, i ova studija je pokazala da nema vremenske povezanosti između MMR vakcine i autizma. Treće, ni autizam, ali ni bilo koji drugi poremećaj iz SAP nije povezan sa vakcinacijom (43).

Japanska populaciona studija iz 2005. godine imala je isti cilj – da utvrdi da li postoji povezanost između MMR vakcine i rizika za nastanak autizma. Ključni rezultat ove studije bio je porast kumulativne incidencije SAP sa 47,6 na 10.000 dece koja su rođena 1988. godine, na 117,2 na 10.000 dece rođene 1996. godine. Ono što je najznačajniji i najupečatljiviji nalaz u studiji jeste činjenica da su stope autizma nastavile da rastu i nakon povlačenja MMR vakcine iz upotrebe, i nisu smanjene u petogodišnjem periodu (1988 – 1992) tokom koga je obuhvat imunizacijom opao na samo 69,8%. Ukoliko bi vakcina bila odgovorna za nastanak autizma, pad incidencije bi morao da bude uočljiv nakon povlačenja vakcine. Međutim, kontinurani porast incidencije autizma u suprotnosti je sa navedenim hipotezama. Autori su zaključili da, shodno rezultatima studija iz SAD i Velike Britanije u kojima se MMR vakcina kontinuirano koristi, povlačenje MMR vakcine u Japanu nije dovoljno da zaustavi porast incidencije autizma (44).

Značajni su i rezultati studije slučajeva i kontrola koja je imala za cilj da pokaže da li su deca koja imaju neki od poremećaja iz autističnog spektra bila izložena većem broju antigena koji su sadržani u vakcinama, u poređenju sa zdravom decom. Studija je uključila više od 700 dece bez pervazivnog poremećaja i više od 300 dece sa poremećajem. Sva deca bila su uzrasta 6–13 godina, a rođena između 1994. i 1999. godine. Autori su analizirali izloženost antigenima od rođenja do 3. meseca, od rođenja do 7. meseca i od rođenja do 2. godine života. Takođe, analizirana je i ukupna izloženost tokom čitavog perioda. Pokazano je da deca koja su bila izložena većoj koncentraciji antigena tokom jednog dana, ili čak tokom čitavog perioda nisu bila u većem riziku od nastanka autizma. Takođe, pokazano je da porast izloženosti antigenima i rizik za nastanak autizma u srazmernom odnosu. Izlaganje dece većem broju imunogena tokom prve godine života ne povećava rizik za nastanak autizma, niti bilo kog drugog pervazivnog poremćaja (45).

Najznačajniji dokaz da ne postoji povezanost između MMR vakcine i rizika za nastanak autizma dali su sistematski pregled literature iz 2012. godine (46), koji je uključio 57 epidemioloških studija, sa 14.700.000 dece i meta-analiza iz 2013. godine, koja je uključila 5 kohortnih i 5 studija slučajeva i kontrola (47). Rezultati meta-analize su pokazali da ni komponente vakcine (timerosal ili živa), kao ni aplikovanje polivalentne vakcine (MMR) ne nose rizik od nastanka bilo kog poremećaja iz spektra autizma.

Retrospektivna kohortna studija, koja je sprovedena u SAD-u 2015. godine, obuhvatila je više od 95.000 dece koja su imala stariju braću i sestre sa ili bez pervazivnog poremećaja. Studija je imala je za cilj da proceni frekvenciju poremećaja iz autističnog spektra među decom koja su imala, tj. nisu imala brata ili sestru sa ovim poremećajem. Pokazano je da MMR vakcina nije povezana sa rizikom od nastanka autizma, nezavisno od toga da li je dete imalo brata ili sestru kod kojih je prethodno postavljena dijagnoza nekog od poremećaja iz ovog spektra (48).

Etiologija autizma

I ako etiologija autizma nije sasvim razjašnjena, postoje snažni dokazi o prisustvu neurobiološke osnove sa značajnom genetskom komponentom kod obolelih, kao i moguća interakcija između gena i prenatalne životne sredine. Utvrđeno je da kod obolelih od autizma postoje sheme dezorganizacije korteksa u većini uzoraka, a dezorganizacija je prisutna u onim delovima koji su zaduženi za socijalno i emocionalno funkcionisanje, komunikaciju i jezičke sposobnosti. Ovakve abnormalnosti mogu predstavljati set razvojnih neuropatoloških karakteristika koje su u osnovi autizma, a verovatno su rezultat disregulacije i diferencijacije neurona u prenatalnim stadijumima razvoja (49).

Prema najnovijim leteraturnim podacima, morfološke promene mozga u uzrastu 6-12 meseci, dakle, pre dobijanja MMR vakcine, prethode kliničkom ispoljavanju autizma. Studija je upoređivala decu koja imaju porodični rizik za nastanak pervazivnog poremećaja sa decom kod koje je taj rizik mali. Pokazano je da je volumen

mozga, tj.njegov ekscesivni rast povezan sa pojavom i težinom simptoma koji se sreću u okviru pervazivnog poremećaja. Algoritam koji je uključio površinu mozga dobijenu sa magnetne rezonance dece uzrasta 6-12 meseci predviđao je dijagnozu autizma kod dece uzrasta 2 godine, sa pozitivnom prediktivnom vrednošću od 81% i senzitivnošću od 88%. Ovi rezultati ukazuju na činjenicu da se promene mozga koje prethode ispoljavanju kliničkih simptoma pervazivnog poremećaja dešavaju još tokom ranog razvoja (50).

Epidemiološka situacija morbila

Još od vremena kada je dr *Wakefield* objavio rezultate svoje studije i doveo u vezu MMR vakcinu i autizam, obuhvat MMR imunizacijom počeo je da opada, bez obzira na mnogobrojne studije koje su iznele obilje dokaza da MMR vakcina ne povećava rizik od nastanka autizma. Ukoliko se analiziraju podaci SZO i obuhvat imunizacijom MMR vakcinom na globalnom nivou, zapaža se da je on u 2016. godini iznosio svega 85%, što je nedovoljno da se održi dovoljno visok nivo kolektivnog imuniteta i spreče epidemije morbila. Imunizacija u ovom trenutku prevenira 2 do 3 miliona smrtnih ishoda svakoga dana. Sa druge strane, ukoliko bi se obuhvat imunizacijom povećao, to bi sprečilo dadatnih 1,5 miliona smrtnih ishoda. Takođe, procenjeno je da u svetu 19,5 miliona dece nije dobilo obavezne vakcine (51).

U našoj zemlji, obuhvat imunizacijom je drastično opadao, počev od 2013. godine sa više od 92% na svega 81% koliko je iznosio tokom 2016. godine. U prvoj polovini 2017. godine obuhvat MMR vakcinacijom iznosio je samo 34,6%, tj. za prethodnih 7 godina opao je za čak 77,5%. Naravno, to je dovelo do povećanja obolevanja od morbila, što je posebno izraženo 2014. i 2015. godine kada su stope incidencije iznosile 0,51 na 100.000 i 5,35 na 100.000, u poređenju sa 2013. godinom kada je stopa incidencije iznosila samo 0,01 na 100.000.

Od početka oktobra 2017. godine, zaključno sa 14. 2. 2018. godine na teritoriji Republike Srbije, uključujući i teritoriju nadležnosti Zavoda za javno zdravlje Kosovska Mitrovica, registrovana su ukupno 2222 slučaja malih boginja, od kojih je 1138 laboratorijski potvrđeno u Institutu Torlak. Pet osoba je umrlo zbog komplikacija ove bolesti (52).

Zaključak

Prevalencija autizma je poslednjih decenija u porastu, ali ovaj porast može da se objasni bar jednim delom promenama u dijagnostičkim kriterijumima i porastom svesti o poremećaju, kako kod lekara, tako i kod roditelja i osoba koje su uključene u obrazovanje deteta. Rezultati brojnih epidemioloških studija, publikovani u eminentnim medicinskim časopisima, idu u prilog hipoteze da MMR vakcina ne povećava rizik za nastanak autizma. MMR vakcina je visoko efektivna u prevenciji morbila.

Napomena
Rad je izlagan na mini simpozijumu "Proslava 70 godina Instituta i Katedre za epidemiologiju Medicinskog fakulteta Univerziteta u Beogradu", na 46. simpozijumu Stremljenja i novine u medicini, Medicinski fakultet u Beogradu, 12.12.2017. godine.

LITERATURA

1. Matson JL, Boisjoli JA. Differential diagnosis of PDDNOS in children. RASD. 2007; 1:75-84.
2. Diagnostic and Statistical Manual of Mental Disorders (DSM IV). Fourth Edition. Am J Psychiatry. Washington DC. 2013.
3. Charman T, Baird G. Practitioner review: Diagnosis of autism spectrum disorder in 2- and 3-year-old children. J Child Psychol Psychiatry. 2002; 43(3):289-305.
4. Rondeau E, Klein LS, Masse A, Bodeau N, Cohen D, Guile´ JM. Is pervasive developmental disorder not otherwise specified less stable than autistic disorder? A meta-analysis. J Autism Dev Disord. 2011; 41:1267–1276.
5. Lord C. Follow-up of two-year-olds referred for possible autism. J Child Psychol Psychiatry. 1995; 36(8):1365-1382.
6. Van Daalen E, Kemner C, Dietz C, Swinkels SHN, Buitelaar JK, Van Engeland H. Inter-rater reliability and stability of diagnoses of autism spectrum disorder in children identified through screening at a very young age. European child & adolescent psychiatry. 2009; 18:663-674.
7. Olmsted D, Blaxill M. Leo Kanner's mention of 1938 in his report on autism refers to his first patient. J Autism Dev Disord. 2016; 46(1):340-341.
8. Lotter V. Epidemiology of autistic conditions in young children. Social Psychiatry. 1966; 1(3):124-135.
9. Rutter M. Aetiology of autism: findings and questions. J Intellect Disabil Res. 2005; 49(1):231-238.
10. Treffert DA. Epidemiology of infantile autism. Arch Gen Psychiatry. 1970; 22(5):431-438.
11. Fombonne E. Epidemiology of pervasive developmental disorders. Pediatr Res. 2009; 65(6):591-598.
12. Rice CE, Rosanoff M, Dawson G, Durkin MS, Croen LA, Singer A, et al. Evaluating changes in the prevalence of autism spectrum disorders. 2012; 34(2):1-22
13. Rutter M. Incidence of autism spectrum disorders: changes over time and their meaning. Acta Pediatric. 2005; 94(1):2-15
14. Baird G, Simonoff E, Pickles A, Chandler S, Loucas T, Meldrum D et al. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). Lancet. 2006; 368:210–215.
15. Bertrand J, Mars A, Boyle C, Bove F, Yeargin-Allsopp M, Decoufle P. Prevalence of autism in a United States population: the Brick Township, New Jersey, investigation. Pediatrics. 2001; 108:1155–1161.
16. Baron-Cohen S, Scott FJ, Allison C, Williams J, Bolton P, Matthews FE, et al. Prevalence of autism-spectrum conditions: UK school-based population study. Br J Psychiatry. 2009; 194:500-509.
17. Centers for Disease Control and Prevention. Autism Spectrum Disorder (ASD). Autism and Developmental Disabilities Monitoring (ADDM) Network. 2016.
18. Baio J. Prevalence of Autism Spectrum Disorders — Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008. Morbidity and Mortality Weekly Report (MMWR). Surveillance Summaries. 2012; 61(SS03):1-19.

19. Rice C. Prevalence of autism spectrum disorders: Autism and Developmental Disabilities Monitoring Network, United States, 2006. Morbidity and Mortality Weekly Report. 2009; 58(SS10):1–20.
20. Rice C, Braun KVN. Autism and Developmental Disabilities Monitoring Network, and Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders—Autism and developmental disabilities monitoring network, six sites, United States, 2000; Prevalence of autism spectrum disorders—Autism and developmental disabilities monitoring network, 14 sites, United States, 2002; and Evaluation of a methodology for a collaborative multiple source surveillance network for autism spectrum disorders—Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2002. Washington, DC: U.S. Government Printing Office; 2007.
21. Maenner MJ, Rice CE, Arneson CL, Cunniff C, Schieve LA, Carpenter LA, et al. Potential impact of DSM-5 criteria on autism spectrum disorder prevalence estimates. JAMA Psychiatry. 2014; 71(3):292–300.
22. Shattuck PT, Durkin M, Maenner M, Newschaffer C, Mandell DS, Wiggins L, Lee LC, Rice C, Giarelli E, Kirby R. Timing of identification among children with an autism spectrum disorder: Findings from a population-based surveillance study. J Am Acad Child Adolesc Psychiatry. 2009; 48(5):474–483.
23. Durkin MS, Bilder DA, Pettygrove S, Zahorodny W. The validity and usefulness of public health surveillance of autism spectrum disorder. Autism. 2014; 19(1):118–119.
24. Fombonne E. A wrinkle in time: From early signs to a diagnosis of autism. J Am Acad Child Adolesc Psychiatry. 2009; 48(5):463–464.
25. Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcı´n C, et al. Global prevalence of autism and other pervasive developmental disorders. Autism Research. 2012; 5(3):160–179.
26. Hill AP, Zuckerman K, Fombonne E. Epidemiology of autism spectrum disorders. In Volkmar VR, Rogers SJ, Paul R, Pelphrey KA (Eds.). Handbook of autism and pervasive developmental disorders. Diagnosis, development, and brain mechanisms, 4th ed, Wiley, New York, 2014.
27. Montiel-Nava C, Pen˜a JA. Epidemiological findings of pervasive developmental disorders in a Venezuelan study. Autism. 2008; 12(2):191–202.
28. Pantelis PC. Kennedy DP. Estimation of the prevalence of autism spectrum disorder in South Korea, revisited. Autism. 2015; 1-11.
29. Weintraub K. Autism counts. Nature. 2011; 479(7371):22-24.
30. Kim YS, Lenethal BL, Koh YL, Fombonne E, Laska E, Lim EC, et al. Prevalence of autism spectrum disorders in a total population sample. Am J Psychiatry. 2011; 168(9):904–912.
31. King M, Bearman, P. Diagnostic change and the increased prevalence of autism. Int J Epidemiol. 2009; 38(5):1224–1234.
32. King MD, Bearman PS. Socioeconomic status and the increased prevalence of autism in California. Am Sociol Rev. 2011; 76(2):320–346.
33. King MD, Fountain C, Dakhlallah D, Bearman PS. Estimated autism risk and older reproductive age. Am J Public Health. 2009; 99(9):1673–1679.
34. Wakefield AJ, Murch SH, Anthony A, Linell J, Casson DM, Malik M, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet. 1998; 351:637-641.
35. DeStefano F, Chen RT. Negative association between MMR and autism. Lancet. 1999; 353(9169):1987-1978.
36. Taylor B, Miller E, Farrington CP, Petropoulos MC, Favot-Mayaud I, Li J, et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. Lancet. 1999; 353(9169):2026-2029.
37. Dales L, Hammer SJ, Smith NJ. Time trends in autism and in MMR immunization coverage in California. JAMA. 2001; 285(9):1183-1185.
38. Sathyanarayana Rao TS, Andrade C. The MMR vaccine and autism: Sensation, refutation, retraction, and fraud. Indian J Psychiatry. 2011; 53(2):95-96.
39. Murch SH, Anthony A, Casson DH, Malik M, Berelowitz M, Dhillon AP, et al. Retraction of an interpretation. Lancet. 2004; 363(9411):750.
40. Horton R. A statement by the editors of The Lancet. Lancet. 2004; 363(9411):820-821.
41. Eggertson L. Lancet retracts 12-year-old article linking autism to MMR vaccines. CMAJ. 2010; 182(4):E199-200.
42. Kaye JA, del Mar MeleroMontes M, Jick H. Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis. BMJ. 2001; 322:460-462.
43. Meldgaard Madsen M, Hviid A, Vestergaard M, Schendel D, Wohlfahrt J, Thorsen P, et al. A population-based study of measles, mumps and rubella vaccination and autism. NEJM. 2002; 347(19):1477-1482.
44. Honda H, Shimizu Y, Rutter M. No effects of MMR withdrawal on the incidence of autism: a total population study. J Child Psychol Psychiatry. 2005; 46(6):572-579.
45. DeStefano F, Price CS, Weintraub ES. Increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines is not associated with risk of autism. J Pediatr. 2013; 163(2):561-567.
46. Demicheli V, Rivetti A, Debalini MG, Di Pietrantonj C. Vaccines for measles, mumps and rubella in children. Cochrane Database Syst Rev. 2012; 15(2):CD004407.
47. Taylor LE, Swerdfeger AL, Eslick GD. Vaccines are not associated with autism: An evidence-based meta-analysis of case-control and cohort studies. Vaccine. 2014; 32:3623-3629.
48. Jain A, Marshall J, Buikema A, Bnacroft T, Kelly JP, Newschaffer CJ. Autism occurrence by MMR vaccine status among US children with older siblings with and without autism. JAMA. 2015; 313(15):1534-1540.
49. Stoner R, Chow ML, Boyle MP, Sunkin SM, Mouton PR, Roy S. Patches of disorganization in the neocortex of children with autism. NEJM. 2012; 370(13):1209-1219.
50. Hazlett HC, Gu H, Munsell BC, Kim SH, Styner M, Wolff JJ. Early brain development in infants at high risk for autism spectrum disorder. Nature. 2017; 542:348-351.
51. Immunization coverage. World Health Organization. Available from: http://www.who.int/mediacentre/factsheets/fs378/en/
52. Nepublikovani podaci Instituta za javno zdravlje Srbije „Dr Milan Jovanović Batut".

[1]Institut za onkologiju i radiologiju Srbije, Beograd, Srbija
[2]Medicinski fakultet, Univerzitet u Beogradu, Beograd, Srbija

PEDIATRIC RADIOTHERAPY DEPARTMENT - RECOMMENDATIONS FOR OPTIMAL INFRASTRUCTURE AND PERSONNEL

PEDIJATRIJSKO RADIOTERAPIJSKO ODELJENJE – PREPORUKE ZA OPTIMALNU INFRASTRUKTURU I KADAR

Marina Nikitović[1,2], Dragana Stanić[1]

Summary

In multidisciplinary treatment of malignant diseases in pediatric population, radiotherapy with or without surgery, represents the basic modality of local treatment. Although the basic principles of radiotherapy in children are the same as in adults, it has its own specificity because it is applied to an organism in the phase of growth and development. Also, pediatric tumors differ from tumors in adults, so pediatric radiation oncologist has to have knowledge of pediatric oncology. Treatment of children with malignant diseases requires coordinated work of a multidisciplinary team: radiation oncologist, pediatrician, various specialty surgeons, pathologists, each of whom participates in the decision making on combined oncological treatment. Treatment decisions are necessary made in a multidisciplinary environment with the necessary knowledge of all members of the pediatric oncology team.

Pediatric radiation oncology has its specifics and requirements in terms of infrastructure and organization. The basic requirements apply to rooms, equipment, staff, and procedures. Based on the international recommendations, the necessary radiotherapy equipment and its number, for the work with children, is defined. In the treatment of children it is recommended to use 3D conformal radiotherapy, or other advanced techniques, in order to avoid the irradiation of healthy tissues as much as possible. Monitoring early and late unwanted effects of radiotherapy is of great importance in treating children with malignant tumors. Also, a certain level of knowledge in the pathology of malignant diseases of children is necessary of all the members of radiotherapy team.

Pediatric radiotherapy, as an extremely sophisticated and complex method of treatment, can therefore only be performed in hospitals and centers that can meet all of the above high standards and recommendations with the coordinated work of a multidisciplinary team with experience in pediatric oncology.

Key words: pediatric oncology, radiotherapy, department, infrastructure

Sažetak

U multidisciplinarnom lečenju malignih bolesti pedijatrijske populacije, radioterapija sa ili bez hirurgije, predstavlja osnovni modalitet lokalnog lečenja. Iako su osnovni principi radioterapije dece isti kao i kod odraslih, ona ima svoje specifičnosti jer se primenjuje u organizmu koji je u fazi rasta i razvoja. Takođe, tumori dece se razlikuju od tumora odraslih te pedijatrijski radijacioni onkolog mora da ima znanje iz pedijatrijske onkologije. Lečenje dece sa malignim bolestima zahteva koordinisan rad multidisciplinarnog tima: radijacioni onkolog, pedijatar, hirurzi različitih specijalnosti, patolog, od kojih svaki na svoj način učestvuje u donošenju odluke o kombinovanom onkološkom lečenju. Odluke o lečenju je neophodno donositi u multidisciplinarnom okruženju sa neophodnim znanjima svih članova tima iz pedijatrijske onkologije.

Pedijatrijska radijaciona onkologija ima svoje specifičnosti i zahteve u pogledu infrastrukture i organizacije. Osnovni zahtevi se odnose na prostorije, opremu, osoblje i izvođenje procedura. Na osnovu internacionalnih preporuka definisana je neophodna radioterapijska oprema za rad sa decom, kao i njen broj. Pri tretmanu dece preporučuje se korišćenje 3D konformalne radioterapije ili drugih naprednih tehnika, da bi se izbeglo ozračivanje zdravih tkiva u što većoj meri. Praćenje ranih i kasnih neželjenih efekata radioterapije je od velike važnosti kod lečenja dece sa malignim tumorima. Takođe, neophodan je određeni nivo znanja iz patologije malignih bolesti dece od strane svih članova radioterapijskog tima.

Pedijatrijska radioterapija, kao izrazito sofisticiran i složen način lečenja, može se stoga obavljati samo u bolnicama i centrima koji mogu zadovoljiti sve navedene visoke standarde i preporuke uz koordinisan rad multidisciplinarnog tima sa iskustvom u pedijatrijskoj onkologiji.

Ključne reči: pedijatrijska onkologija, radioterapija, odeljenje, infrastruktura

Uvod

Rezultati lečenja dece obolele od maligniteta su u značajnom poboljšanju. Ukupno preživljavanje dece i adolescenata sa malignitetom se povećalo sa 58% na 81% od 1975.godine (1,2). Napredak koji je ostvaren, i koji se još uvek ostvaruje, postignut je zahvaljujući stalnoj saradnji multidisciplinarnih timova, ne samo unutar jedne države već između centara u velikom broju država.

Terapija dece sa malignitetom je intenzivna, dugotrajna i kompleksna. Lečenje dece sa malignim bolestima zahteva koordinisan rad multidisciplinarnog tima: pedijatar, hirurzi različitih specijalnosti, patolog, radijaci-

oni onkolog, od kojih svaki na svoj način učestvuje u donošenju odluke o kombinovanom onkološkom lečenju. Odluke o lečenju je neophodno donositi u multidisciplinarnom okruženju sa neophodnim znanjima svih članova tima iz pedijatrijske onkologije (3,4). Pri izboru tretmana mora se uzeti u obzir i rizik od komplikacija koje utiču na ukupno preživljavanje i smanjuju kvalitet života (5). Dobar rezultat se može postići samo timskim radom lekara, drugog medicinskog osoblja i ostalih stručnjaka uključenih u lečenje dece u odgovarajućim uslovima.

U multidisciplinarnom lečenju malignih bolesti pedijatrijske populacije, radioterapija sa ili bez hirurgije, predstavlja osnovni modalitet lokalnog lečenja. Iako su osnovni principi radioterapije dece isti kao i kod odraslih, ona ima svoje specifičnosti jer se primenjuje u organizmu koji je u fazi rasta i razvoja (6). Takođe, tumori dece se razlikuju od tumora odraslih, te pedijatrijski radijacioni onkolog mora da ima znanja iz pedijatrijske onkologije. Stoga, deca se moraju lečiti u radioterapijskim centrima sa značajnim iskustvom u ovoj oblasti. Terapija zračenjem je ključna za uspešno lečenje pedijatrijskih tumora mozga, kao i drugih solidnih tumora (7).

Rad pedijatrijskog radioterapijskog odeljenja zahteva koordinisan rad multidisciplinarnog tima: radijacionog onkologa, pedijatra, medicinskog fizičara, anesteziologa i radioterapijskog tehničara, u odgovarajućem okruženju uz primenu adekvatne opreme i procedura. Postoje internacionalne preporuke za optimalnu infrastrukturu, kojih se treba pridržavati pri planiranju, izgradnji i svakodnevnom radu pedijatrijskog radioterapijskog odeljenja (8-11).

Mreža upućivanja i pristup pedijatrijskoj radioterapiji

Odavno je poznato da optimalna terapija za decu, adolescenate i mlade odrasle sa malignitetom treba da se sprovodi u specijalizovanim ili „referentnim centrima“ (12). Broj i lokalizacija referentnih centara zavisi od populacionih karakteristika i geografije zemlje. Za visoko specijalizovane terapijske opcije, kao što je pedijatrijska radioterapija, preporučuje se preusmeravanje bolesnika iz manjih u veće centre. Neophodno je uspostaviti nacionalnu mrežu koja olakšava upućivanje dece sa dijagnostifikovanom malignom bolešću u najiskusnije specijalizovane centre sa pedijatrijskom radioterapijom. Mora se stvoriti svest o postojanju pedijatrijske radioterapije kod pedijatrijskih i adultnih onkologa širom zemlje. Treba omogućiti pristup radioterapijskim centrima obezbeđivanjem besprekornih puteva za upućivanje, smeštaj i podršku pedijatrijskim pacijentima.

Preporučuje se obezbeđivanje privremenog smeštaja ambulantnim pacijentima i njihovim porodicama, blizu jedinice za lečenje (tzv.“Roditeljske kuće”). Svest o dostupnosti ovih usluga treba objaviti široj javnosti i svim lekarima.

Partnerstva sa drugim pedijatrijskim radioterapijskim centrima

Preporučeno je uspostavljanje partnerstva između pedijatrijskih jedinica radioterapije i sličnih centara u drugim razvijenim zemljama, kako bi se olakšale konsultacije, telekonferencije, delili obrazovni resursi i klinički protokoli. Poželjno je uspostaviti program razmene između takvih institucija u cilju obuke lekara i drugog osoblja. Takođe, zbog relativno malog broja pedijatrijskih onkoloških pacijenata, neophodno je uključivanje dece u klinička istraživanju kroz nacionalne ili međunarodne multinacionalne kooperativne grupe (13). Ovo predstavlja jedan od uslova da se dobiju podaci koji se mogu porediti i ostvare slični rezultati lečenja u pedijatrijskoj onkologiji u svakom od centara. Sva deca se moraju lečiti prema najboljem dostupnom kliničkom protokolu.

Opšte prihvaćen stav je da se ovaj princip najbolje obezbeđuje na odeljenjima koja su aktivna u kliničkim ispitivanjima i procesima registracije malignitеta. Ukoliko postoji mogućnost, detetu treba ponuditi šansu da učestvuje u relevantnim kliničkim studijama, čiji je cilj poboljšanje optimalnog terapijskog pristupa za sve obolele. Terapija dece i adolescenata sa malignitetom se konstantno usavršava. Preporuke za terapijski protokol se moraju redovno ažurirati, u skladu sa savremenim naučnim zaključcima.

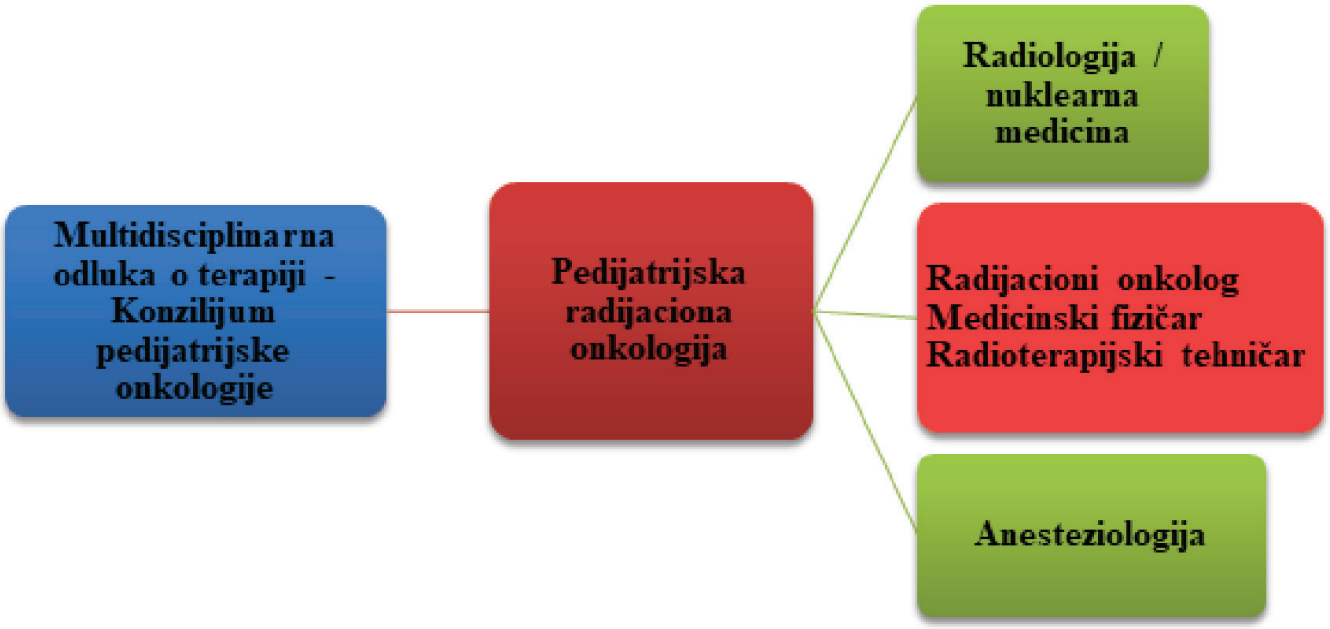
Infrastruktura pedijatrijske radioterapije

Pedijatrijska radijaciona onkologija ima svoje specifičnosti i zahteve u pogledu infrastrukture i organizacije. Osnovni zahtevi se odnose na prostorije, opremu, osoblje i izvođenje procedura (8,10).

- **Objekti:** Zgrada i infrastruktura prostorija u kojima se obavlja radioterapija dece bi trebala biti adekvatna i prilagođena lečenju pedijatrijskih pacijenata (8). Pored prostorija za primpremu i izvodjenje radioterapijskog tretmana - prostorija za simulator zračne terapije, megavoltažni bunker, neophodne su prostorije za planiranje radioterapije od strane lekara i medicinskih fizičara, kao i prostorija za skladištenje i izradu imobilizacionih sredstava. Pored prostora za preglede i konsultacije lekara, neophodan je prostor za uvođenje i oporavak dece od anestezije, kao i igraonice za decu. Neophodan je pristup optimalnom izvođenju dijagnostikih radioloških procedura, kao i procedura nuklearne medicine. Takođe, potrebne su optimalne službe laboratorije i patologije, kao i prostor za psihologa i socijalnog radnika.

- **Oprema:** Na osnovu internacionalnih preporuka definisana je neophodna radioterapijska oprema za rad sa decom, kao i njen broj (10,11). Prilikom pripreme dece za izvođenje radioterapije koristi se oprema za pozicioniranje i imobilizaciju, koja je neophodna radi reproducibilnosti terapijskog položaja. Pored mašina kao što su Ro/CT simulator zračenja sa laserskim sistemom, megavoltažni linearni accelerator elektrona (LINAC) putem koga se izvodi zračna terapija, određeni centri raspolažu i brahiterapijskim, kao i protonskim aparatima. Svi aparati su povezani jedinstvenim softverskim sistemom za planiranje zračenja. U svakodnevnoj upotrebi je i oprema za dozimetriju i osiguranje kvaliteta u radioterapiji (9,10).
- **Osoblje:** U pedijatrijskoj onkologiji je neophodan multidisciplinaran rad i donošenje odluka. Pokazano je da dete sa malignitetom ima najveću šansu da preživi ukoliko je dijagnostikovano i lečeno od strane ekspertskog tima lekara, medicinskih sestara i drugih specijalista koji rade na specijalizovanim odeljenjima. Tim mora da obuhvati specijalno edukovane članove koji se bave dijagnostikom i lečenjem: iskusne medicinske sestre, psihologe za podršku pacijenta i porodice, socijalnog radnika i učitelja, i da bude dostupan sve vreme. Pedijatrijski hirurg, neurohirurg, anesteziolog, patolog, radijacioni onkolog i pedijatar, kao i specijalizovane medicinske sestre moraju biti dostupni već u vreme postavljanja dijagnoze, što omogućava brzo započinjanje odgovarajuće terapije i dovodi do maksimalnog smanjenja toksičnosti i komplikacija terapije. Prilikom izvođenja procedura radioterapije veoma je bitna saradnja radijacionog onologa, medicinskog fizičara, radioterapijskih tehničara, kao i anestezilоga, koji su svi specijalizovani i obučeni za rad sa decom. Stvaranje i razvoj kliničkih timova se postiže obezbeđivanjem stalnog profesionalnog usavršavanja i edukacije svih članova tima. Radijacioni onkolog treba da prođe posebnu obuku iz oblasti pediatrijske radioterapije tokom specijalizacije ili tokom boravka u kvalifikovanom centru sa kojim postoji saradnja. Važno je da stručnjaci pedijatrijske radijacione onkologije steknu uvid u strategiju i rezultate lečenja prisustvujući internacionalnim sastancima i kongresima i imaju pristup objavljenoj literaturi (14). Tim mora biti sposoban da odgovori na različite potrebe bolesnika i članova porodice, tokom hospitalizacije ali i tokom faze praćenja.
- **Tehnike:** Savremene tehnike zračenja podrazumevaju precizno planiranje i isporuku doze na volumen mete. Tokom planiranja zračne terapije u volumen mete, pored tumora, standardno se uključuju i zdrava tkiva i organi koji se nazivaju organi pod rizikom (hipofiza, kohlea, temporalni lobusi, optička hijazma, zdravo moždano tkivo, srce, pluća, bubrezi, creva, itd.). Prilikom tretmana dece sa malignitetom, u većini situacija, preporučuje se korišćenje 3D konformalne radioterapije (3D CRT) ili drugih naprednih tehnika planiranja i isporuke zračenja, putem kojih je omogućeno smanjenje izloženosti normalnih tkiva zračenju. Pri savremenom planiranju radioterapije, koriste se preporuke koje pored tumorske doze i frakcionisanja, definišu i odnos doze i volumena organa pod rizikom uključenih u zračni volumen (15). Neophodno je poznavanja prednosti i mana svih dostupnih modaliteta radioterapije: konvencionalne i naprednijih fotonskih tehnika zračenja, stereotaksične radioterapije (SRT), inetenzitetom modulisane radioterapije (IMRT), protonske i terapije teškim jonima; da bi se doneo konačan izbor u svakom pojedinačnom slučaju.
- **Izvođenje:** U odnosu na tretman odraslih, priprema i izvođenje radioterapije kod dece zahteva mnogo više vremena. Medicinsko osoblje mora da roditeljima dece sa malignitetom da sveobuhvatnu informaciju o dijagnozi i terapiji njihovog deteta, kao i

Shema 1. Radioterapijska infrastruktura - kadar



mogućim neželjenim efektima tretamana, uključujući i psiho-socijalni savet. Sve informacije i planovi moraju biti dobro dokumentovani i jasno objašnjeni roditeljima (16). Ove informacije moraju biti saopštene roditeljima koji daju pristanak na predloženi plan u skladu sa nacionalnim propisima. Na sličan način treba informisati i dete, u skladu sa njegovim godinama i moći shvatanja, dete takođe može da da pristanak na plan terapije ili bar da se složi sa njim. Dodatno, treba detaljno diskutovati o dijagnozi, terapiji i krajnjem ishodu, ali imajući u vidu uzrast deteta i nivo razumevanja. Svakom detetu ili adolescentu sa malignitetom, kao i njegovoj porodici treba ponuditi psihološku podršku. Psihološka priprema deteta putem različitih pisanih, audio- ili video materijala i razgovora, a kod jako male dece neophodna procedura anestezije prilikom izvodjenja zračenja, predstavljaju specifičnosti pedijatrijske radijacione onkologije. Pri radu, radioterapijski centri treba da se pridržavaju internacionalnih principa radiološke zaštite i osiguranja kvaliteta (9-11).

- **Praćenje:** Dugoročno praćenje dece sa malignitetom je ključno ne samo za praćenje preživljavanja nego i kvaliteta života i kasnih posledica terapije. Za svakog bolesnika posebno treba osmisliti plan praćenja i učestalost kontrola, u zavisnosti od rizika za relaps bolesti i ispoljavanje toksičnosti, i dogovoriti detalje sa roditeljima. Način praćenja zavisi od biologije tumora i vrste primenjene terapije. Neželjeni efekti radioterapije su smanjeni povećanjem konformalnosti naprednih tehnika zračenja i smanjivanjem margina volumena mete (17,18). Praćenje ranih i kasnih neželjenih efekata radioterapije je od velike važnosti pri lečenju dece sa malignim tumorima, čemu treba posvetiti posebnu pažnju i vreme. Preporučuje se redovno praćenje sve tretirane dece tokom i nakon primene radioterapije, kako bi se dijagnostikovao relaps bolesti, sekundarni maligni tumori (19), komorbiditeti i komplikacije, kao akutne i kasne toksičnosti radioterapijskog tretmana. Neophodno ozračivanje zdravih struktura može dovesti do kasnih sekvela u vidu oštećenja kognitivne, endokrine funkcije, oštećenja sluha, vida, itd.(20-22). Radi poređenja sa drugim centrima preporučuje se korišćenje međunarodno prihvaćenih skorova za beleženje i izveštavanje o toksičnosti radioterapije (23). Istraživanja su pokazala da su najznačajniji faktori od kojih zavisi toksičnost radioterapije uzrast deteta, doza zračne terapije i opseg zračnog volumena (24). Preporučuje se da da se praćenje obavlja u istom medicinskom centru i nakon određene granice za pedijatrijsku dob (25).

Budućnost pedijatrijske radioterapije

Ostvarivanje realnih prognoza za buduće infrastrukturne potrebe pedijatrijske radioterapije je teško. Faktori koji mogu uticati ne uključuju samo epidemiološke podatke, kao što su broj pedijatrijkih onkoloških pacijenata i procenat dece tretirane radioterapijom, već i faktore kao što su promene u indikacijama, koje je mnogo teže predvideti. Još jedan faktor koji značajno utiče na potrebnu infrastrukturu radioterapije je uvođenje sofisticiranijih i ujedno zahtevnijih tehnika, koje se uglavnom koriste u pedijatrijskoj radijacionoj onkologiji, što će sve dovesti do povećane potrebe za opremom i osobljem.

Zaključak

Odeljenje za pedijatrijsku radioterapiju ima specifične zahteve u pogledu infrastrukture i osoblja. Za optimalan rad sa decom neophodan je multidisciplinarni tim posvećen pedijatrijskoj onkologiji (radijacioni onkolog, medicinski fizičar, radioterapijski tehničar, pedijatar, pedijatrijski anesteziolog), sa obrazovanjem u oblasti pedijatrijske onkologije. Pedijatrijska radioterapija, kao izrazito sofisticiran i složen način lečenja, može se obavljati samo u bolnicama i centrima koji mogu zadovoljiti sve navedene visoke standarde i preporuke.

Napomena
Rad je usmeno izložen na mini simpozijumu "Savremeni principi pedijatrijske onkologije", na 46. simpozijumu Stremljenja i novine u medicini, Medicinski fakultet u Beogradu, 13.12.2017.godine.

LITERATURA

1. Ward E, DeSantis C, Robbins A, et al. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin. 2014;64:83–103.
2. Hammond D. Progress in the study, treatment and cure of the cancers of children. In: Burchenal JH, Oehgen HF, eds. Cancer Achievement, Challenges, and Prospects for the 1980s. New York, NY: Grune & Stratton; 1981:171–190.
3. Meek RS. Pediatric oncology: the team approach of the medical center of Delaware. Del Med J. 1988;60:169–172, 177–178.
4. Labotka RJ. Book review of principles and practice of pediatric oncology. JAMA. 2002;288:894–895.
5. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2009;101:946–958.
6. American Academy of Pediatrics. Guidelines for the pediatric cancer center and role of such centers in diagnosis and treatment. Pediatrics. 1986;77:916–917.
7. American Cancer Society. Special section: cancer in children and adolescents. In: Cancer Facts and Figures 2014. Atlanta, GA: American Cancer Society; 2014.
8. IAEA. Recommendations for pediatric radiotherapy programmes – Minimal requirements of quality. Pediatric Radiation Oncology: Bridging the gap Viena, June 2013.
9. IAEA. Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards. Interm Edition. IAEA Vienna, 2011.
10. IAEA. Radiation Protection in Pediatric Radiology, Safety Report Series No.71. IAEA Vienna, 2012.
11. IAEA. Setting up a Radiotherapy Programme: Clinical, Medical Physicist, Radiation Protection and Safety Aspects, IAEA, Vienna 2008.
12. Kramer S, Meadows AT, Pastore G, et al. Influence of place of treatment on diagnosis, treatment, and survival in 3 pediatric solid tumors. J Clin Oncol. 1984;2:917–923

13. Cohen ME, Duffner PK, Kun LE, et al. The argument for a combined cancer consortium research data base. Cancer. 1985;56:1897–1901
14. Constine LS, Donaldson SS. Pediatric radiation oncology: subspecialty training? Int J Radiat Oncol Biol Phys. 1992;24:881–884.
15. Bentzen SM, Constine LS, O. Deasy J, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): An Introduction to the Scientific Issues. Int J Radiat Oncol Biol Phys. 2010; 76(3suppl): S3–S9.
16. Dickens M. Miracles of Courage: How Families Meet the Challenge of a Child's Critical Illness. New York, NY: Dodd, Mead; 1985.
17. SanFilippo A. Late mortality rates have declined in pediatric cancer survivors. HemOnc today. 2015;16:1, 10–11.
18. Changes in pediatric cancer treatments yield reduced late mortality. ASCO Daily News. Wrap up edition; 2015:2
19. Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2006;98:1528–1537.
20. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Eng J Med. 2006;355:1572–1582.
21. Merchant TE, Kiehna EN, Li C, et al. Radiation dosimetry predicts IQ after conformal radiation therapy in pediatric patients with localized ependymoma. Int J Radiat Oncol Biol Phys 2005;63(5):1546-54.
22. Bass JK, Hua CH, Huang J, et al. Hearing Loss in Patients Who Received Cranial Radiation Therapy for Childhood Cancer. J Clin Oncol 2016;34(11):1248-55.
23. NCI-CTCAE Version 4.0 US Department of health and human services – NIH. NCI, June 2010.
24. Merchant TE, Conklin HM, Wu S, et al. Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. J Clin Oncol. 2009;27:3691–3697.
25. Mulrooney DA, Neglia JP, Hudson MM. Caring for adult survivors of childhood cancer. Curr Treat Options Oncol. 2008;9:51–66.

Srpsko lekarsko društvo, Beograd, Srbija

INFORMATION TECHNOLOGY IN MEDICINE IN THE 21ST CENTURY

INFORMACIONE TEHNOLOGIJE U MEDICINI 21. VEKA

Dragica Kosi

Summary

We are witnessing a lot of unimaginable achievements in information and nanotechnology, and their application in modern medicine which can be considered a revolution in medicine.

"Is it radical transformation through innovation?", as asked Jozef Schumpeter, and how does conventional medicine respond to these challenges? How did it begin, and how long did information technology arrive? With this paper we tried to give at least a partial answer.

So far a doctor, we can conditionally say, was the only bearer of medical knowledge - medical information, in his hands was a "general database" (professional literature), as well as a database of personal, medical data (medical card of the patient). However, now the situation is completely different.

Digitization of medicine and networking, and absolute availability of knowledge, as well as electronic records, represent the systematic storage of a large number of medical findings, quick and targeted search and usability of information about a particular person, and immense help to the doctor. The introduction of algorithms enables the lightning processing of incoming information. However, "knowledge from a computer" can be a danger to the availability of information to lay people, which makes it necessary to verify the validity of the information source. The new concept of "transferring and disseminating knowledge from a computer" aims to transfer responsibility for personal health.

In the development of nano technology, two critical moments are: decryption of DNA (genome analysis, to details reveals the "biology" of a person) and micro-sensors and wireless transmission technologies that are integrated into an innovative mobile phone (smartphone) that allows monitoring of a number of vital parameters. Miniature ultrasound devices and powerful micro-analyzers, in smartphones and virtual browsing are a reality. Does the doctor lose the ground under his feet? What is the general attitude of patients towards innovation? The answers to these questions are very different, and we tried to present them with the track of the facts pro et contra.

With the conclusion about the undeniable contribution and benefits of innovative technologies in medicine, there are many open questions. We wanted to mention and discuss some of the dilemmas related to information technology and nano technology.

Key words: information technology, nano technology, availability of information; databases, data processing, algorithms, microanalysers, smartphones

Sažetak

Svedoci smo doskora nezamislivih dostignuća u informacionim i nano tahnologijama, a njihova primena u savremenoj medicini može se smatrati revolucijom u medicini.

„Da li je u pitanju radikalna transformacija kroz inovacije?", kako je naveo ovaj problem Jozef Šumpeter, i kako da konvencionalna medicina odgovori na ove izazove? Kako je započela, i dokle je stigla informaciona tehnologija? Ovim radom smo pokušali da damo makar delimični odgovor.

Doskora je lekar, možemo uslovno reći, bio jedini nosilac medicinskog znanja – medicinskih informacija, u njegovim rukama je bila i „opšta baza podataka" (stručna literatura), kao i baza ličnih, medicinskih podataka (zdravstveni karton pacijenta). Međutim, sada je situacija u potpunosti drugačija.

Digitalizacija medicine i „umrežavanje mreža" odnosno apsolutna dostupnost znanja, kao i elektronski karton predstavljaju sistematično skladištenje velikog broja medicicinskih nalaza, brzu i ciljanu pretragu i upotrebljivost informacija o konkretnoj osobi, i neizmernu pomoć lekaru. Uvođenje algoritama omogućuje munjevitu obradu prispelih informacija. Ipak, „znanje iz kompjutera" može biti opasnost u dostupnosti informacija laicima, zbog čega je neophodna provera validnosti izvora informacija. Novi koncept „prenošenja i širenja znanja iz kompjutera" ima za cilj da na svakog pojedinca prenese deo odgovornosti za lično zdravlje.

U razvoju nano tehnologija dva su presudna momenta: dešifrovanje DNK (analiza genoma, do detalja otkriva „biologiju" osobe) i mikrosenzori i tehnologija bežičnog prenosa, koji su objedinjeni u inovativnom mobilnom telefonu (smartfonu) koji omogućuje praćenje niza vitalnih parametara. Minijaturni uređaji ultrazvuka i moćni mikroanalizatori, u „pametnim telefonima" i virtuelni pregled je danas realnost. Gubi li time lekar tlo pod nogama? Kakav je uopšte stav pacijenata prema inovacijama? Odgovori na ova pitanja su veoma različiti, a pokušali smo da ih predstavimo sledom činjenica pro et contra.

Uz zaključak o neospornom doprinosu i koristi od inovacionih tehnologija u medicini, ostaju mnoga otvorena pitanja. Radom smo želeli da navedemo i razmatrimo neke od dilema vezanih za informacione tehnologije i nano tehnologije.

Ključne reči: informacione tehnologije, nano tehnologije, dostupnost informacija; baze podataka, obrada podataka, algoritmi, mikroanalizatori, smartfon

Uvod

Budućnost u medicini je već počela. U literaturi i stručnoj javnosti nalazimo zanimljive, uzbuđujuće, ali i donekle zabrinjavajuće podatke o dostignućima u informacionim i nano tehnologijama, i njihovoj primeni u savremenoj medicini.

Da li je u pitanju potpuna rekonstrukcija medicine? „Radikalna transformacija kroz inovacije“ kako kaže Jozef Šumpeter (1,2). Zapravo, to je “gradnja na starim temeljima ali novim materijalima” prema rečima Erika Topol-a (2).

Kako će se to odraziti na ulogu lekara u budućnosti, a kako na kvalitet zdravstvene zaštite. Kako da konvencionalna medicina odgovori na ove izazove (3)? Ovo je pokušaj da se na ta pitanja odgovori.

Medicina kao nauka zasnovana na dokazima

Za početak bi trebalo protumačiti kako je započela i dokle je stigla informaciona tehnologija (IT). Početak ove priče mogao bi biti poduhvat Gutemberg – a (3, 4). To je prva revolucija u svetu informacija (ne računajući pronalazak pisma). Od tada informacije (u tom periodu je to bila knjiga) više nisu privilegija uskog kruga ljudi, i njihova dostupnost se širila do današnjih - neverovatnih razmera. Time je najavljen početak nezadrživog procesa, u kome razvoj IT (sada i nano tenologija) medicinskoj praksi nude neslućene mogućnosti.

Dosada se medicina, uglavnom, zasnivala na dokazima iz kliničkih ispitivanja u populaciji (zaključivanje po zakonu velikih brojeva), ne uzimajući u obzir lične osobenosti pojedinačnog pacijenta, a još manje podatke iz njegove porodične anamneze (3). Ta nova saznanja bila su opšta i - primenjivana su na svakoga. Da li je to u redu? Izabrani lekar je bio taj koji je, jedini, o svemu vodio računa – fokusiran na svog pacijenta, on je primenjivao ta znanja „po meri pacijenta“ (5).

Tačno je da dokazi ostaju siguran temelj, ali je doktor važna karika, jer upravo on primenjuje dokazana medicinska znanja na konkretnoj osobi (pacijentu).

Doskora je lekar, možemo uslovno reći, bio jedini nosilac medicinskog znanja, u njegovim rukama je bila i „opšta baza podataka“ tj. stručna literatura, kao i baza ličnih, medicinskih podataka (zdravstveni karton pacijenta). No, ovaj relativni procep koji je do sada, bio jedino u nadležnosti lekara, sada dopunjuju nova dostignuća. Digitalizacija medicine i „umrežavanje mreža“ ostvarila je apsolutnu dostupnost znanja, a elektronski karton (EK), sa svim medicinskim nalazima (čak i mogućim nalazima genetskih pretraga), ličnom i porodičnom anamnezom, omogućava sistematično skladištenje, brzu i ciljanu pretragu i upotrebljivost informacija, o konkretnoj osobi.

NOVI KONCEPT – “*PATIENT CENTRED APPROCH*”

Novi koncept – “*Patient centred approach*”, kao i “*Individual approach*” (5) – je nesumnjiv napredak moderne medicine. Napretkom u polju medicine pružaju se mnogostruke pogodnosti za pacijenta. Uzmimo za primer uvođenje algoritama i drugih moćnih „analitičkih alata“ (5) koji dalje omogućuje munjevitu obradu prispelih informacija što rezultira *output*-om: dijagnozom (sa detaljnim podacima o bolesti), i dalje, nudi se izbor opcija tretmana (lečenja) za svaki konkretan slučaj (5). No, da li je sve ovo dovoljan uslov (masa deponovanih podataka i moćna obrada) da medicinu, procenu zdravlja, i odlučivanje o lečenju, prepustimo mašini? Da, rekli bismo, ali samo ukoliko je supervizor lekar.

Za laike, koji olako prihvataju i prepuštaju se „znanju sa interneta“, opasnost je u dostupnosti informacija - nudi se „medicina“ iz nekompetentnih izvora, i iste takve informacije o bolesti, i što je još gore - o lečenju.

Da pomenemo i opasnost od sajberhondrije (3), čovek modernog doba, iscrpen stresom, frustriran, „dekompenzovan“, sugestibilan - na sebe primnjuje „stečeno znanje“ i prisvaja ponuđene simptome, a „pronađe“ na sebi i poneki „znak“ bolesti.

Lekari već imaju iskustvo u suočavanju sa ovim problemima; na njima je da ukažu da samo lekar može, iz mnoštva delova, pravilno da sklopi tu složenu slagalicu: zdravlje - bolest. Uprkos prednostima koje nude elektronski mediji, pre svega internet, lekar je još uvek jedino merodavan za dijagnostikovanje i lečenje.

U suprotnom pacijent bi mogao biti gubitnik, i lekar je dužan da ga upozna sa tim rizikom (pre I iznad svega, zbog dobrobiti pacijenta). Ipak treba reći da ovaj novi koncept - „prenošenja, širenja znanja“, ima za cilj da učini dostupnim informacije od značaja za zdravlje i prevenciju bolesti. Time se na neki način, na svakog pojedinca prenosi deo odgovornosti za lično zdravlje. Informisani pojedinac razvija svest o značaju zdravlja, očekivano je da će bolje voditi brigu o očuvanju svog zdravlja, kontrolisati svoje zdravlje, i time postati najbolji saradnik u timu sa lekarom, na putu ka zajedničkom cilju – zdravlju.

Nano tehnologije

Krajem prošlog veka, informacione i nano tehnologije su na široka vrata ušle u medicinsku nauku. Beleže se dva presudna momenta:

- Mobilna, bežična tehnologija (telefonija), kroz neograničen pristup informacijama i komunikaciji, mikrosenzori u pametnim telefonima, sasvim su izmenili živote ljudi,
- Dešifrovanje DNK je izazvalo revoluciju u biologiji (Ljudski genom više nije kamen iz Rozete, genom je konačno dešifrovani hijeroglif (6, 7)

„Nešto epsko se upravo dešava - eksponencijalno unapređenje medicine je u toku“ po rečima Jeremy Howard (8).

Ovo je rezime 20. veka. Doprinos navedenog napretku medicine je, doskora bio, nezamisliv. Genomika nam, analizom genoma, do detalja otkriva „biologiju“ osobe, njene metaboličke karakteristike, zatim potencijalne, skrivene rizike za obolevanje od određene bolesti (od dijabetesa do karcinoma), čak i predvidljivost efekata terapije na konkretnog pacijenta (9).

Uz to, razvoj mikro senzora i tehnologija bežičnog prenosa objedinjena u inovativnom mobilnom telefonu smartfon tehnologije (pametni telefon) pruža neslućene mogućnosti, jer lični medicinski podaci, i njihova obrada, dostupni su gde god postoji mobilni signal (3).

Praćenje niza fizioloških parametara, i posebno važnih vitalnih parametara, koje je bilo moguće meriti jedino u ordinaciji doktora, ili bolničkom okruženju, sada možemo meriti kod kuće, i pratiti promene tokom dnevnih aktivnosti (3). Kontinuitet praćanja i visok nivo tačnosti, ranije smo nalazili samo u jedinicama intenzivne nege. Sada je merenje, kao što je krvni pritisak, srčani ritam i brzina protoka krvi, zasićenje krvi kiseonikom, kompletna biohemijska analiza krvi, nivo hormona stresa, i još mnogo toga, dostupno zahvaljujući mikrosenzorima u mobilnom telefonu (prototip je već izrađen) (10).

Šta sve ovo donosi pacijentu i kolika je dobrobit za njega? Primera radi, ukoliko znamo da neko ima genetski rizik za dijabetes (ili već ispoljenu bolest), može se kontinuirano koristiti senzor glukoze, i u skladu sa tim preduzimati sve preporučene mere, da bi se sprečilo ispoljavanje bolesti. Ako bolest već postoji, nalazi mogu da upozore na nezadovoljavajuću regulaciju, i da treba korigovati terapiju (ili preduzeti druge mere - fizičku aktivnost, dijetu i sl.) (2).

Isto tako, pojedinac sa početnom hipertenzijom, ili sa genetskom predispozicijom za nju, može svoj krvni pritisak pratiti kontinuirano, tako može uočiti i dnevne događaje koji utiču na krvni pritisak, i u skladu s tim, prilagoditi svoje aktivnosti ili korigovati terapiju.

Revolucionarne promene u medicini

Verovatno jedna od najvećih promena je usledila uvođenjem minijaturnih uređaja ultrazvuka koji su zamenili „ikonu medicine“ – stetoskop (2). Može se reći da je i to „prevaziđeno“. Moćni mikroanalizatori, u „pametnim telefonima“, daju detaljnu analizu svake supstance (npr. hrane), ili kožne promene, koja se stavi „u fokus“. Dovoljno je usmeriti kameru, recimo, na hranu – i već dobijamo spektar analizu biohemijskog sastava. Doktori sa Stanford Univerziteta stvorili su algoritam za dijagnostikovanje raka kože, a potom ga testirali – uporedili sa nalazima dvadeset jednog sertifikovanog dermatologa. Algoritam odgovara sposobnostima kliničara da pravilno identifikuju maligne i benigne lezije (10). Tehnološki napredak sada omogućava brzu sekvencu genoma patogena pomoću alata kod pacijenata sa sumnjom na sepsu. Rana dijagnoza putem sekvenciranja može u budućnosti zameniti potrebu za kulturom krvi, a znamo da dva ili više dana kašnjenja u čekanju rezultata hemokulture može odneti život (10).

Čak je i virtuelni pregled - realnost. Mikrokamere u smartfonu su do te mere usavršene da snimaju, npr. ušni kanal i bubnu opnu, dalje je tu sliku moguće elektronski proslediti specijalisti ORL – ovaj virtuelni pregled omogućava da doktor postavi dijagnozu i odredi lečenje, bez direktnog kontakta sa pacijentom. Isto važi za pregled oka i druge brojne organe gde je takođe moguće uz on line kontakt sa odgovarajućim specijalistom postaviti dijagnozu (10).

Postoji i mogućnost da se svi ovi nalazi, umesto doktoru, preusmere u programe sa moćnom analitičkom obradom, koji mogu rezultirati dijagnozom i preporukom za lečenje (11, 12).

Gubi li time lekar tlo pod nogama? Da li će algoritam zameniti lekara (13)?

„Šta će se desiti sa mnom - Da li će me ove stvari zameniti“ – pitanja su koja se nameću lekaru modernog doba (3).

Da li je na pomolu vreme, u kome će doktor čekati da bude prozvan: „Pacijent će vas sada primiti“ kako duhovito zaključuje bard modernog doba medicine dr Erik Topol (3).

Odgovor na ovo pitanje uslediće nakon što razmotrimo sledeće: Kakav je stav pacijenata prema svim ovim inovacijama? Slobodno se može reći veoma različit. Evo činjenica: pro et contra. Sjajna je mogućnost da su lični medicinski podaci dostupni gde god postoji mobilni signal. Svako će, dakle, u svakom trenutku, moći da ima sve medicinske informacije, kao i sve svoje medicinske nalaze, mnogi to podržavaju, ali da li svi to žele (2, 3)? Pre svega stariji pacijenti to teže prihvataju, za mnoge čak ne bi bilo dobro da su „umreženi“ i da se njihovi vitalni znaci neprekidno emituju na njihovim pametnim telefonima, stalno „osluškivanje“ bi moglo imati nepoželjne posledice. Ipak, mnogo je veća dobrobit ako pacijent bude na vreme upozoren na porast glikemije ili na pojavu malignih poremećaja ritma (2, 3).

To je prepoznato kao značajna prednost, i u jednoj anketi je potvrđeno da većina ljudi, čak 80% osoba, želi da u svakom trenutku, ima svoje podatke, i da može da prati svoje vitalne parameter. Uslov je da su podaci pouzdani, stručno analizirani, da su bezbedni, i da je pri-

vatnost zagarantovana (3). Može li to garantovati sistem IT? Potvrđuje se da može. No, svedoci smo „upada“ i „obaranja“ sajtova Vlada, svetskih finansijskih magnata, velikih „sigurnih“ banaka. Ipak, ostaje nam da verujemo da je moguć visok stepen sigurnosti medicinskih podataka. Pre svega, verujemo u to da je doktor nezamenjiv, sa stvarnim pregledom umesto virtuelnog, i u realnom vremenu umesto elektronskom poštom ili web kamerom.

Umesto zaključka

Uz zaključak o neospornom doprinosu i koristi od inovacionih tehnologija i njihove primene u medicini, ostaju mnoga pitanja:

- pitanje sigurnosti poverljivih, ličnih medicinskih podataka;
- opasnost od nepouzdanih izvora;
- opasnost od sajberhondrije,
- pitanje izostanka neposrednog, živog kontakta sa lekarom, i posebno terapijskog učinka tog kontakta

Kao i krucijalna pitanja (na koja se odgovori sami nameću):

- Dovodi li koncept „digitalizacija medicine“ u pitanje autonomiju i autoritet lekara?
- Da li se nekim „prečicama“ i „mašinskim učenjem“ koje je dostupno svima, mogu nadoknaditi klasične studije medicine?
- Da li je pristup bazama medicinskih podataka od strane laika, dovoljan za potpuno razumevanje složenog medicinskog fenomena bolesti?
- Baze podataka daju tačne, ali fragmentirane informacije, koje su „umrežavanjem“ povezane, i daju pouzdane algoritme, ali nemaju mogućnost doživljaja stvarne osobe koja ima zdravstveni problem
- Šta je sa mnoštvom interakcija i specifičnosti samog organizma, koje su ključne za ispoljavanje medicinskog fenomena bolesti? Znamo da ne postoji „ista bolest“ kod dve osobe obolele od nominalno „iste bolesti“

I nakon svih iznesenih argumenata: Znači li to da bi svako mogao sesti na sudijsku stolicu - otvoriti kompjuter i početi da sudi (14)?

Može se pretpostaviti da će u sledećem veku, istoričari medicine navoditi upravo ove teme, i ovaj trenutak, kao najdramatičniji potres u istoriji medicine.

LITERATURA:

1. Dodgson M, Gann D. Joseph's Schumpeter's Gales of Creative Destruction. In: Dodgson M, Gann J. (editors). Innovation: A Very Short Introduction. Oxford University Press; 2010.
2. Topol E. Creative Destruction of Medicine: How the Digital Revolution Will Create Better Health Care. New York: Basic Books; 2013.
3. Topol E. The Patient Will See You Now: The Future of Medicine is in Your Hands. New York: Basic Books; 2015.
4. Topol E. Why Medical Gutenberg is Important for Clinicians. Medscape (serial on the Internet). 2013 Feb (cited 2017 Dec). Available from: https://www.medscape.com/viewarticle/778828
5. Flanagan T. One Size Doesn't Feet All: Personalized Healthcare and Genomic Medicine. HealthCare Recruiters International. 2016 May (cited 2017 Dec). Available from: http://www.hcrnetwork.com/one-size-doesnt-fit-personalized-healthcare-genomic-medicine/
6. Genetic Health (homepage on the Internet). London: A Life Decoded. 2008 Aug (cited 2017 Dec). Available from: http://www.genetic-health.co.uk/media/genome.pdf
7. Larkin M. Dr Eric Topol: Digital healthcare will put the patient in charge. 2014 October (cited 2017 Dec). Available from: https://www.elsevier.com/connect/Dr-Eric-Topol-Digital-healthcare-will-put-the-patient-in-charge
8. Dorrier J. Exponential Medicine: Deep Learning Al Better Than Your Doctor at Finding Cancer. SingularityHub (serial on the Internet). 2015 Nov (cited 2018 Jan). Available from: https://singularityhub.com/2015/11/11/
9. Genomics Research from Technology Networks (homepage on the Internet). Sudbury: Bioinformatics Program Rides Wave of DNA Revolution in Medical Science, Health Care. 2011 Dec (cited 2018 Jan). Available from: https://www.technologynetworks.com/genomics/news/bioinformatics-program-rides-wave-of-dna-revolution-in-medical-science-health-care-188347
10. Topol E. Eric's Topol Top 10 Tech Advances Shaping Medicine. Medscape (serial on the Internet). 2018 Jan (cited 2018 Feb). Available from: https://www.medscape.com/viewarticle/890982
11. Topol E. Topol on 5 Devices Physicians Need to Know About. Medscape (serial on the Internet). 2012 Jun (cited 2017 Dec). Available from: https://www.medscape.com/viewarticle/765017
12. Jung AK. Book Review: Creative Destruction of Medicine: How the Digital Revolution Will Create Better Health Care. Healthc Inform Res. 2013 Sep; 19(3): 229–231.
13. Topol E. Topol on Replacing Clinicians With Algorithms. Medscape (serial on the Internet). 2013 July (cited 2017 Dec). Available from: https://www.medscape.com/viewarticle/805212
14. Creative Destruction of Medicine (homepage on the Internet). **Vartabedian B.** Praise for The Creative Destruction of Medicine. Cited 2017 Dec. Available from: http://creativedestructionofmedicine.com/?p=2

[1]Institut za Higijenu sa medicinskom ekologijom, Medicinski fakultet, Univerzitet u Beogardu, Beograd, Srbija
[2]Bolnica za ginekologiju i akušerstvo, Kliničko-bolnički centar Zemun, Beograd, Srbija

FACTORS INFLUENCING INTERNET ADDICTION

FAKTORI KOJI UTIČU NA ZAVISNOST OD INTERNETA

Nikolina Banjanin[1], Nikola Banjanin[2]

Summary

Using the Internet is a part of everyday life. The Internet is used for various purposes such as obtaining information, communication, education, entertainment.

Some of the factors that influence Internet addiction are gender, neuroticism, using the Internet every day.

Today it would be difficult to imagine life without the Internet, but it should find a measure in the use of the Internet.

Keywords: Internet use, factors, Internet addiction

Sažetak

Korišćenje interneta predstavlja deo svakodnevnice. Internet se koristi u različite svrhe kao što su pribavljanje informacija, komunikacija, edukacija, zabava.

Neki od faktora koji utiču na zavisnost od interneta su pol, neurotičnost, korišćenje interneta svaki dan.

Danas bi život bez interneta bilo teško zamisliti, međutim treba naći meru u njegovom korišćenju.

Ključne reči: korišćenje interneta, faktori, zavisnost od interneta

Uvod

Zavisnost od interneta predstavlja veliki problem današnjice. Internet koriste osobe različitih životnih dobi: deca, adolescenti, odrasli. Odrasli veoma često koriste internet zbog prirode posla koji obavljaju, te je za njih korišćenje interneta postalo gotovo neizbežno. Takođe, internet predstavlja sredstvo za pribavljanje informacija, komunikaciju i zabavu (1). Stoga, internet pruža različite mogućnosti kao što su čitanje vesti, čitanje o zdravstvenim problemima, slušanje muzike, gledanje filmova, igranje igrica, pisanje imejlova i odgovaranje na imejlove, prikupljanje stručnih i naučnih informacija, plaćanje računa, kupovinu preko interneta i komuniciranje sa ljudima koji žive u inostranstvu.

Pristup internetu moguć je na različitim mestima: kod kuće, u školama, u kafićima, u restoranima, na poslu. Sveprisutna dostupnost interneta dovela je do toga da ljudi značajan deo svog vremena u toku dana provode upravo na internetu i zbog toga zapostavljaju svoje obaveze. Tako, mladi zanemaruju svoje obaveze u školi, u kući, prema roditeljima i prijateljima. Neretko se dešava da dolazi do smanjenja uspeha u školi, dobijanja nižih ocena i neredovnog pisanja domaćih zadataka. Pored zanemarivanje obaveza, zavisnost od interneta može da dovede i do različitih štetnih uticaja po zdravlje čoveka.

Ljudi se zahvaljujući postojanju mnogobrojnih društvenih mreža učlanjuju u različite grupe na osnovu sličnih interesovanja i na taj način međusobno povezuju i razmenjuju svoje ideje. Društvene mreže omogućuju i postavljanje svojih fotografija, fotografija sa letovanja i zimovanja i sa različitih proslava; potom postavljanje obaveštenja o različitim događajima, reklamiranje različitih proizvoda, iskazivanje svog trenutnog raspoloženja, dopisivanje, postavljanje različitih pesama, filmova, različitih vesti, članaka iz novina kao i deljenje informacija o različitim dešavanjima u svom životu. Vreme provedeno na internetu veoma često postaje zamena za druženje sa prijateljima uživo, šetnju, bavljenje fizičkom aktivnošću, odlazak na koncerte, u bioskop, u pozorište.

Laka dostupnost interneta i sve veća popularnost društvenih mreža čiji je broj u stalnom porastu doveli su do značajne izmene u načinu života ljudi kao i njihove komunikacije. Ipak, iako internet predstavlja značajno sredstvo za komunikaciju između ljudi dešava se da se osobe koje više koriste internet osećaju usamljenije, otuđenije i neraspoloženije i da su veoma često povučene u sebe.

Zavisnost od interneta predstavlja značajan problem današnjice, te se velika pažnja posvećuje istraživanju uzroka zavisnosti od interneta, faktora koji utiču na zavisnost od interneta kao i prevenciji zavisnosti od interneta.

Uticaj različitih faktora na zavisnost od interneta

Različita istraživanja su se bavila ispitivanjem korišćenja interneta, različitih aktivnosti na internetu, korišćenjem društvenih mreža kao i ispitivanjem zavisnosti od interneta. Značajna pažnja u studijama data je ispitivanju faktora koji utiču na zavisnost od interneta.

Pol je jedan od važnih činilaca koji utiče na zavisnost od interneta. Rezultati istraživanja navode da zavisnost od

interneta nije podjednako zastupljena kod oba pola. Naime, studija sprovedena kod adolescenata u Kini pokazala je da je zavisnost od interneta više zastupljena kod muškaraca nego kod devojaka. Takođe, pokazano je da su adolescenti koji koriste društvene mreže, igraju igrice na internetu i kupuju putem interneta imali veću prevalenciju blage i teške zavisnosti od interneta u odnosu na adolescente koji nisu uključeni u te aktivnosti (2). I druge studije su istraživale uticaj igranja igrica na zavisnost od interneta i pokazale da je igranje igrica aktivnost koja ima značajan uticaj na zavisnost od interneta. Naime, rezultati studije sprovedene u Japanu pokazali su da je igranje igrica internet aktivnost koja je najviše povezana sa rizikom za zavisnost od interneta (3). Takođe, i rezultati studije sprovedene u Kini pokazali su da igranje igrica ima veliki uticaj na zavisnost od interneta (4).

Rezultati sprovedenih istraživanja navode da su faktori rizika za zavisnost od interneta pored muškog pola (5,6,7,8) i život sa samo jednim roditeljem (6). Međusobni odnosi između roditelja takođe imaju uticaj na zavisnost od interneta. Tako, navodi se da su faktori rizika za zavisnost od interneta konflikti između roditelja (9).

Dalje, i stepen uhranjenosti i različite navike korišćenja interneta imaju značajnu ulogu. Pokazano je da gojaznost, korišćenje interneta svaki dan i korišćenje interneta više od dva sata dnevno imaju uticaj na zavisnost od internet (10). Važan uticaj ima i korišćenje pametnih telefona i anksioznost (8). Potom, od značaja su i hiperaktivnost (11), neurotičnost (12) i psihijatrijska oboljenja (5). Neka istraživanja posvetila su pažnju i istraživanju uticaja životne sredine na zavisnost od interneta. Pokazano je da je urbana sredina značajan faktor rizika za zavisnost od interneta (13, 14). Od značaja je i sklapanje novih poznanstava preko interneta (15). Uloga majke i porodice je od posebnog značaja za nastanak zavisnosti od interneta. Roditelji bi značajan deo vremena trebalo da provedu sa svojom decom i ukažu im na sve potencijalne prednosti i mane korišćenja interneta. Rezultat istraživanja je pokazao da su adolescenti čije su majke domaćice ređe zavisni od interneta (16).

Istraživanje sprovedeno kod studenata medicine pokazalo je da su usamljenost i interpersonalni problemi jaki prediktori zavisnosti od interneta dok uzrat i pol nisu (17). I druge studije ukazuju da osećanje usamljenosti povećava rizik za nastanak zavisnosti od interneta (10,18). Takođe, nađena je i pozitivna povezanost između depresije i zavisnosti od interneta (19).

Važnu ulogu ima i socioekonomski status. Naime, studija sprovedena u Koreji pokazala je da je u provincijama sa nižim socioekonomskim statusom zavisnost od interneta zastupljenija (20).

Usled prekomernog korišćenja interneta dešava se veoma često da je spavanje zamenjeno provođenjem vremena na internetu. Posledično dolazi do nedostatka adekvatnog odmora, pada koncentracije, promena raspoloženja, povećanja rizika za saobraćajne neseće, smanjenja produktivnosti rada. Problemi povezani sa prekomernom upotrebom interneta postali su ozbiljni te je planiranje i implementacija prevencije i mera kontrole hitno potrebna (21).

Zaključak

Život bez interneta bi danas bilo teško zamisliti. Zbog brojnih mogućnosti koje pruža internet je postao sastavni deo života ljudi. Internet se koristi u različite svrhe, a aktivnosti na internetu zbog kojih ljudi predominantno provode vreme su različite.

Međutim, veoma je važno naći meru u korišćenju interneta. Internet treba koristiti na odgovarajući način kako bi se sprečio nastanak zavisnosti od interneta i nastanak mnogih štetnih efekata interneta na zdravlje čoveka.

Potom, adekvatnim korišćenjem interneta moglo bi se sprečiti zapostavljanje porodičnih i profesionalnih obaveza kao i zamena vremena spavanja korišćenjem interneta.

Navedeni rezultati istraživanja pokazali su da na zavisnost od interneta uticaj imaju mnogobrojni faktori kao što su pol, vrsta aktivnosti na internetu, porodični odnosi, stepen uhranjenosti, navike korišćenja interneta, mentalno zdravlje, sredina u kojoj ljudi žive kao i socioekonomski status.

Zahvaljujući poznavanju činilaca koji imaju bitan uticaj na zavisnost od interneta moguće je sprovesti odgovarajuće mere prevencije zavisnosti od interneta.

Literatura

1. Tsitsika A, Critselis E, Kormas G, Filippopoulou A, Tounissidou D, Freskou A, Spiliopoulou T, Louizou A, Konstantoulaki E, Kafetzis D. Internet use and misuse: a multivariate regression analysis of the predictive factors of internet use among Greek adolescents. Eur J Pediatr 2009; 168(6):655-665.
2. Xin M, Xing J, Pengfei W, Houru L, Mengcheng W, Hong Z. Online activities, prevalence of Internet addiction and risk factors related to family and school among adolescents in China. Addict Behav Rep 2017; 7:14-18.
3. Tsumura H, Kanda H, Sugaya N, Tsuboi S, Takahashi K. Prevalence and Risk Factors of Internet Addiction Among Employed Adults in Japan. J Epidemiol 2018;28(4):202-206.
4. Jiang Q, Huang X, Tao R. Examining Factors Influencing Internet Addiction and Adolescent Risk Behaviors Among Excessive Internet Users. Health Commun 2018;33(12):1434-1444.
5. Wu CY, Lee MB, Liao SC, Chang LR. Risk Factors of Internet Addiction among Internet Users: An Online Questionnaire Survey. PLoS One 2015;10(10):e0137506.

6. Lau JTF, Gross DL, Wu AMS, Cheng KM, Lau MMC. Incidence and predictive factors of Internet addiction among Chinese secondary school students in Hong Kong: a longitudinal study. Soc Psychiatry Psychiatr Epidemiol. 2017; 52(6):657-667.
7. Prabhakaran MC, Patel VR, Ganjiwale DJ, Nimbalkar MS. Factors associated with internet addiction among school-going adolescents in Vadodara. J Family Med Prim Care 2016;5(4):765-769.
8. Choi SW, Kim DJ, Choi JS, Ahn H, Choi EJ, Song WY, Kim S, Youn H. Comparison of risk and protective factors associated with smartphone addiction and Internet addiction. J Behav Addict 2015; 4(4):308-14.
9. Ko CH, Wang PW, Liu TL, Yen CF, Chen CS, Yen JY. Bidirectional associations between family factors and Internet addiction among adolescents in a prospective investigation. Psychiatry Clin Neurosci. 2015; 69(4):192-200.
10. Koyuncu T, Unsal A, Arslantas D. Assessment of internet addiction and loneliness in secondary and high school students. J Pak Med Assoc 2014; 64(9):998-1002.
11. Critselis E, Janikian M, Paleomilitou N, Oikonomou D, Kassinopoulos M, Kormas G, Tsitsika A. Predictive factors and psychosocial effects of Internet addictive behaviors in Cypriot adolescents. Int J Adolesc Med Health. 2014; 26(3):369-75.
12. Yan W, Li Y, Sui N. The relationship between recent stressful life events, personality traits, perceived family functioning and internet addiction among college students. Stress Health 2014 ;30(1):3-11.
13. Stavropoulos V, Alexandraki K, Motti-Stefanidi F. Recognizing internet addiction: prevalence and relationship to academic achievement in adolescents enrolled in urban and rural Greek high schools. J Adolesc. 2013;36(3):565-76.
14. Pawłowska B, Zygo M, Potembska E, Kapka-Skrzypczak L, Dreher P, Kędzierski Z. Prevalence of Internet addiction and risk of developing addiction as exemplified by a group of Polish adolescents from urban and rural areas. Ann Agric Environ Med 2015; 22(1):129-36.
15. Krishnamurthy S, Chetlapalli SK. Internet addiction: Prevalence and risk factors: A cross-sectional study among college students in Bengaluru, the Silicon Valley of India. Indian J Public Health 2015; 59(2):115-21.
16. Ahmadi K. Internet addiction among Iranian adolescents: a nationwide study. Acta Med Iran 2014; 52(6):467-72.
17. Simcharoen S, Pinyopornpanish M, Haoprom P, Kuntawong P, Wongpakaran N, Wongpakaran T. Prevalence, associated factors and impact of loneliness and interpersonal problems on internet addiction: A study in Chiang Mai medical students. Asian J Psychiatr 2017; 31:2-7.
18. Wegmann E, Brand M. Internet-Communication Disorder: It's a Matter of Social Aspects, Coping, and Internet-Use Expectancies. Front Psychol 2016; 7:1747.
19. Oh WO. Factors influencing internet addiction tendency among middle school students in Gyeong-buk area. Taehan Kanho Hakhoe Chi 2003; 33(8):1135-44.
20. Lee CS, McKenzie K. Socioeconomic and Geographic Inequalities of Internet Addiction in Korean Adolescents. Psychiatry Investig 2015; 12(4):559-62.
21. Mihara S, Osaki Y, Nakayama H, Sakuma H, Ikeda M, Itani O, Kaneita Y, Kanda H, Ohida T, Higuchi S. Internet use and problematic Internet use among adolescents in Japan: A nationwide representative survey. Addict Behav Rep 2016;4:58-64.

[1]Institute of Pathophysiology "Ljubodrag Buba-Mihailović", Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[2]Institute for cardiovascular disease "Dedinje", Belgrade, Serbia
[3]Institute of Pathophysiology, Faculty of Dental Medicine, University of Belgrade, Belgrade, Serbia
[4]Faculty of Medicine, University of Belgrade, Belgrade, Serbia

CHRONIC LOW GRADE INFLAMMATION IN AGING PROCESS AS A LINK ON A CHAIN OF OBESITY - RELATED VASCULAR DISORDERS

HRONIČNA NISKOSTEPENA INFLAMACIJA U PROCESU STARENJA KAO KARIKA U LANCU VASKULARNIH POREMEĆAJA KOJI SU POVEZANI SA GOJAZNOŠĆU

Danijela Vučević[1], Đorđe Radak[2,4], Drago Đorđević[1], Maja Miletić[3], Aleksandar Jakovljević[3], Bojan Jorgačević[1], Milena Vesković[1]

Summary

The pathogenesis of obesity-related vascular disorders has not been fully elucidated. The fundamental role of inflammation in aging process is now widely recognized, particularly for atherosclerotic disease which begins before birth. The number of obese individuals worldwide has reached two billion, leading to an explosion of obesity-related vascular disorders associated with increased morbidity and mortality. Obesity, as a chronic low grade inflammatory process, is important risk factor for metabolic and cardiovascular disease. Despite a well-known genetic component, this risk appears to originate from several abnormalities in adipose tissue function associated with a chronic inflammatory state. In particular, obesity as the most common nutritional disorder in industrialized countries, is closely related to impaired endothelial function, a well-known marker of preatherosclerotic disease. These conditions disrupt vascular homeostasis by causing an imbalance between the nitric oxide pathway and the endothelin-1 system, with impaired insulin-stimulated endothelium-dependent vasodilation. Having in mind the growing population of overweight and obese people worldwide, along with an increasingly aging population, understanding the pathophysiology of obesity on cardiovascular system is essential. The mechanisms linking obesity-related vascular disorders and low grade inflammation in aging process are the focus of this paper.

Keywords: inflammation, aging, obesity-related vascular disorders, insulin resistance, adipokines

Sažetak

Patogeneza vaskularnih poremećaja koji su povezani sa gojaznošću nije u potpunosti razjašnjena. Danas je poznata fundamentalna uloga inflamacije u procesu starenja, naročito kod aterosklerozne bolesti, koja počinje pre rođenja. Broj gojaznih osoba širom sveta je dostigao cifru dva biliona i doveo do "eksplozije" vaskularnih poremećaja koji su povezani sa gojaznošću i povećanim morbiditetom i mortalitetom. Gojaznost, kao hronični niskostepeni inflamacijski proces, je važan faktor rizika za nastanak metaboličkih i kardiovaskularnih bolesti. Pored dobro proučene genetske komponente, izgleda da je za ovaj rizik zaslužno i nekoliko poremećaja funkcije masnog tkiva koji se dovode u vezu sa stanjem hronične inflamacije. U tom smislu prednjači gojaznost, pošto je kao najčešći poremećaj ishrane u razvijenim zemljama blisko povezana sa endotelnom disfunkcijom, koja predstavlja uveliko poznat marker preaterosklerozne bolesti. Takvi uslovi narušavaju vaskularnu homeostazu, dovodeći do dizbalansa između metaboličkog puta azot monoksida i sistema endotelina-1, što je praćeno otežanim odvijanjem insulinom podstaknute vazodilatacije. Imajući u vidu globalni zajednički porast broja kako osoba sa viškom kilograma i gojaznih osoba, tako i starije populacije, razumevanje patogeneze gojaznosti i njenog uticaja na kardiovaskularni sistem je od esencijalnog značaja. Mehanizmi koji čine sponu između vaskularnih poremećaja povezanih sa gojaznošću i niskostepene inflamacije u procesu starenja nalaze se u fokusu ovog rada.

Ključne reči: inflamacija, starenje, vaskularni poremećaji povezani sa gojaznošću, insulinska rezistencija, adipokini

INTRODUCTION

Discovery consists of seeing what everybody has seen and thinking what nobody has thought /Albert Szent-Gyorgyi/.

Inflammatory process is a part of the host immune defenses to pathogens and tissue responses to injury. Inflammatory reactions engage and operate at all levels of biological organization, from free radicals to behavior (1). Inflammation may be considered a core process of human aging because of its involvement in baseline aging and in the major degenerative diseases of later life, atherosclerosis, Alzheimer's disease and cancer (2). Blood levels of C-reactive protein (CRP), interleukin-6 (IL-6) and other proinflammatory cytokines are risk indicators of cardiovascular events and mortality (3). Even in the absence of specific pathological lesions, inflammatory gene expression increases during aging in humans and animal models (1, 3).

The acute phase of inflammation largely involves the innate immune responses, whereas subsequent phases may include adaptive immune responses of antigen-selected T and B cells, but with continuing mediation by various innate immune factors (1). Because tissue

damage activates gene responses shared with the acute phase, most degenerative diseases of aging involve innate immune responses. Thus, it is very difficult to resolve cause and effect in the slow inflammatory processes that may be shared across tissues during chronic degenerative diseases of aging (1-3). Besides, foci of chronic inflammation also typically stimulate local cell proliferation, which in some instances progresses to cellular (proliferative) senescence (1, 4-6).

Obesity is understood as a proinflammatory state with chronic activation of acute phase responses (7-9). Blood CRP and IL-6 are strongly correlated with the degree of obesity across a broad range of the body mass index (BMI) (10). White adipose depots contain numerous macrophages, which secrete proinflammatory cytokines (11). Visceral fat in particular secretes adipokines and IL-6 (12). Adipocytes from diabetics show increased cytokine production, telomere shortening and other markers of senescence (13). The increased blood inflammatory profile in obesity is linked to insulin resistance (IR), diabetes, cardiovascular disease (CVD) and cancer (14).

Table 1. Inflammatory response levels modified according to *Finch, 2010*

Biological level	ROS oxidation of DNA, lipids and proteins; glycooxidation (AGE formation)
Cellular level	activation of macrophages by endotoxins; oxidized proteins, lipids and AGE; autogenous inflammation from replicative cell senescence
Systemic level	humoral elevation of CRP, IL-6 and cytokines; redox shift in glutathione; induction of fever by IL-6 and TNFα; increased basal metabolic rate; lethargy and other sickness behaviors
Environmental	infectious pathogens that cause systemic inflammation and focal lesions; ambient inflammogens from combustion of fossil fuels and tobacco

Abbreviations: ROS-reactive oxygen species; DNA-deoxyribonucleic acid; AGE- advanced glycation end products; CRP- C reactive protein; IL-6 – interleukin 6; TNFα; tumor necrosis factor alpha

Inflammation-associated cellular-molecular damage is recognized as a major feature in aging (3). By-stander damage by reactive oxygen species (ROS) to neighboring cells and molecules is an important source of oxidative damage during aging that interacts with the endogenous damage from free radicals (1-3). The activation of macrophages and neutrophils increases secretion of ROS, which can cause oxidative by-stander damage to deoxyribonucleic acid (DNA) and proteins within a cell and neighboring cells and extracellular proteins (1). Immune activation in response to specific antigens can also have by-stander effects through secretion of interferon γ (IFNγ) and other cytokines that influence the differentiation of neighboring T cells (2). Thus, the oxidized molecules from by-stander damage are recognized by macrophages-through RAGE receptors (receptors for AGE /advanced glycation endproducts/) (15, 16). These transmembrane receptors can stimulate further inflammatory reactions (1). RAGE has broad ligand binding and is a mediator of systemic oxidative stress and inflammatory responses (15-18). Additionally, blood glucose concentration is directly linked to inflammatory changes in many aspects of aging, by driving the formation of AGE, which in turn is directly linked to vascular disease (1). Microbial pathogens also activate RAGE (19).

Obesity, as a chronic low grade inflammatory process, can damaging effects on many organ systems (20, 21). Namely, the number of obese individuals worldwide has reached two billion, leading to an explosion of obesity-related health problems associated with increased morbidity and mortality (20, 22, 23). Many of the comorbid conditions are related to metabolic syndrome (MS), characterized by a visceral (abdominal) obesity, dyslipidemia, glucose intolerance and high arterial blood pressure (24-26). The prevalence of the MS is age-dependent. Advancing age affects all levels of pathogenic components of the MS (27-29). Age-related alterations contributing to the increased prevalence of the MS in elderly subjects is presented in Table 2 (27). Each component of MS is independent cause of cardiovascular events, such as stroke, cardiomyopathy, coronary artery disease (CAD), myocardial infarction, cardiac insufficiency and sudden cardiac death (30). CVD, including heart disease, vascular disease and atherosclerosis, are the most critical global health threat, contributing to more than one-third of the global morbidity (21). CVD is the highest cause of death globally, too (31). In most cases, clinical manifestations of CVD result from atherosclerosis, which was identified as a lipid-storage disease. At the present time, CVD is recognized as a chronic inflammatory condition of the vessel wall, that results from the transendothelial passage (transcytosis) of cholesterol-rich atherogenic Apo-B lipoproteins from the plasma into the intima (21). It is likely that inflammation induced by obesity accelerates the atherosclerosis

Table 2. Age-related alterations contributing to the increased prevalence of the MS in elderly subjects

Alterations	Contribution
Body composition	/
Increased visceral fat	proinflammatory status
Increased fat in muscle and liver	IR
Decreased lean body mass	IR
Immunosenescence	/
Low grade inflammation	IR
Activation of the innate immune system	IR
Receptor signaling alterations	/
Insulin receptor	IR
Toll like receptors	proinflammatory status
	/
Stress	IR and proinflammatory status
Increased oxidative stress	IR
Increased ER stress	IR
Increased adrenal hormones (cortisol, etc.)	IR

Abbreviations: MS-metabolic syndrome; IR-insulin resistance; ER--endoplasmic reticulum

(5, 21, 24, 30, 31). In particular, obesity as the most common nutritional disorder in industrialized countries, is closely related to impaired endothelial function, a well-known marker of preatherosclerotic disease (21, 32). Having in mind the growing population of overweight and obese people worldwide, along with an increasingly aging population, understanding the pathophysiology of obesity on cardiovascular system is essential. The mechanisms linking obesity-related vascular disorders and low grade inflammation in aging process are the focus of this paper.

INFLAMMATORY RESPONSE OF THE VESSEL WALL IN OBESITY

The term endothelial dysfunction refers to a maladapted endothelial phenotype characterized by reduced nitric oxide (NO) bioavailability, increased oxidative stress, elevated expression of proinflammatory and prothrombotic factors, and abnormal vasoreactivity to endothelial-dependent stressor (32). Experimental and clinical data support a link between systemic inflammation and endothelial dysfunction (21, 25, 30, 32, 33). Moreover, endothelial dysfunction has increasingly been recognized to play an important role in a number of conditions associated with a high prevalence of atherosclerotic CVD (21, 25, 30). It is regarded as an early stage of atherosclerosis, which is a chronic inflammatory disease (21).

Foam cells

Experimental atherosclerosis induced by high-cholesterol diet is often associated with pulmonary emphysema (34-37), increased levels of triglycerides (TG) and high concentrations of free fatty acids (FFA) in the blood and lung tissue (34). In rabbits, after a month of hypercholesterolemic diet, aortic lesions become microscopically visible. They are characterized by the accumulation of foam cells in the internal elastic membrane, while the endothelial surface is intact. Foam cells are a characteristic feature in the tissue response associated with bronchial obstruction (34-37).

In an experimental model of atherosclerosis induced by a high-cholesterol diet, monocytes are first cell adjacent to the endothelium. Then they migrate into the subendothelial space, swallow the oxidized cholesterol, and transform it into foam cells (33). Hypercholesterolemia associated with elevated levels of atherogenic lipoproteins (low density lipoprotein /LDL/ and very low density lipoprotein /VLDL/) in the blood, leads to chronic presence of LDL in the arterial wall (21). This condition enhances fatty streaks formation, because lipid migration into the subendothelium is greater than its removal from the arterial wall. It is known that local cytokine secretion and modification of native lipoprotein particles, that are internalized by vascular macrophages via the scavenger receptors class A (SRA) on the surfaces of these cells, lead to the formation of foam cells. Thus, exacerbation of local inflammatory process in the vascular tissue, due to generation of ROS, resulting in further lipoprotein modification and cytokine production (33). It has been shown that mononuclear phagocytic blood cells take part in the phagocytosis of native particles to a lesser extent, and of modified LDL particles to a greater extent after their binding to the SRA. However, these particles may directly migrate into the subendothelium, being subject to phagocytosis, whereas SRA play an important role in the process. These receptors, which mediate the delivery and degradation of modified LDL particles, do not operate on the principle of negative feedback, so even when a large amount of lipid particles is accumulated in the cell, the intake continues, which leads to the formation of foam cells (38). In a state of continuous inflammation, the concentration of LDL particles in blood increases and through the process of passive diffusion they penetrate the arterial intima, where they are trapped by glycosaminoglycans, whereas ROS are being affected as well. LDL particles become highly sensitive to different stimuli, and may be modified by oxidation, glycosylation, or by incorporation into immune complexes. In addition, LDL particles interact with proteoglycans (biglycan and decorin) and form aggregates, with a catalytic activity of sphingomyelinase, cathepsin D, cathepsin F and lysosomal acid lipase (39).

The ability of oxidized LDL molecules (oxLDL) to induce accumulation of cholesterol in macrophages was their first described proatherogenic property. Other proatherogenic effects of oxLDL particles, referring to endothelial cells, include expression of growth factors affecting smooth muscle cells, generation of superoxide anion (O_2), and endothelial cells apoptosis (38). The human endothelial receptor that mediates uptake of oxLDL belongs to C type lecitin family and is referred to as LOX-1 (lecitin-like oxLDL receptor-1) (33). Foam cell formation is also induced by receptors involved in oxLDL uptake (CD34, macrosialin/ CD68 /) and HDL receptor, which is referred to as SB-1 (33).

It is believed that macrophage-colony stimulating factor (M-CSF), interleukin-3 (IL-3) and granulocyte monocyte colony stimulating factor (GM-CSF) play a key role in the process of foam cell formation (40).

Apart from macrophages, foam cell formation is also promoted by vascular smooth muscle cells with properties of lipophages (41).

Preatherosclerotic disease

Numerous animal studies have shown that activation of endothelial cells and expression of specific molecules, responsible for adhesion, migration and accumulation of monocytes and T-lymphocytes, play a crucial role in atherosclerosis (33).

There is evidence that a high cholesterol diet is associated with fast focal expression of vascular cell adhesion molecule-1 (VCAM-1) at predilection sites. In addition, lysophosphatidylcholine, a component of modified lipoprotein, activates VCAM-1 gene transcription in endothelial cells. Lipoprotein(a), however, induces a dose-dependent expression of intercellular adhesion molecule-1 (ICAM-1) on endothelial cells, but it does not affect the expression of VCAM-1 and E-selectin. Furthermore, native LDL molecules, binding to the LDL receptors, increase the concentrations of VCAM-1 and E-selectin in human vascular endothelial cells (41). On the other hand, expression of these molecules is induced and enhanced by tumor necrosis factor alpha (TNFα) and interleukin-1 beta (IL-1β), which originate either from the circulating blood or the vascular wall. These molecules, which are part of the existing local or systemic inflammatory reaction, apart from stimulating the expression of adhesion molecules, lead to changes in procoagulant and fibrinolytic endothelial cells, and the surface of the endothelium becomes thrombogenic. Modifying the properties of endothelial morphology, these cytokines affect the production of NO and prostacyclin, inducing endothelium to synthesize other cytokines, which enhances their proinflammatory activity. IL-1 and TNFα, endothelial cell activators, induce synthesis of specific membrane glycoproteins, redistributing the cytoskeleton of endothelial cells and increasing the synthesis of platelet-activating factor (PAF). PAF is a phospholipid with potential proinflammatory and thrombogenic properties. Its specific significance in atherosclerosis is indicated by the fact that components similar to this phospholipid are present in oxLDL, and that blockade of PAF receptors completely blocks effects of oxLDL molecules on peripheral mononuclear cells, in regard to the secretion of interferon-γ (IFN-γ) and partly to the secretion of TNFα. IL-1 and TNFα also stimulate endothelial cells to produce interleukin-8 (IL-8) that strongly attracts and activates leukocytes. Migration of leukocytes through the morphologically intact endothelium involves direct migration as a response to other cytokines, so-called chemokines. In the early phase of atherogenesis these are monocyte chemotactic protein-1 (MCP-1), localized in atherosclerotic lesions, IL-8, interleukin-16 (IL-16), and C5a-receptor fragment peptide, released in hypercholesterolemia (38, 40).

Inflammatory response has been confirmed to affect accumulation of lipoproteins in the arterial wall. Inflammatory mediators (TNFα, IL-1 and M-CSF) increase the binding of LDL to the endothelium and smooth muscle cells (33). After binding to SRA *in vitro*, modified LDL particles initiate a series of intracellular events, among which activation of urokinase and inflammatory cytokines plays an important role. In this way, due to the presence of lipids, a vicious cycle of inflammation is maintained in the arteries, as well as modification of lipoproteins and continuous inflammation (38, 41). Thus, LDL molecules enhance the expression of SRA on macrophages and in synergy with inflammation facilitate formation of foam cells (41). Also, it should be noted that a large number of activated macrophages is undergoing apoptosis, after which they release lipid content into the matrix and form the lipid nucleus of atheromas (40).

Various studies demonstrate the involvement of immune factors in the etiology of atherosclerosis (21, 25, 33, 38, 40). Apart from antigens responsible for immune responses leading to atherosclerosis, special attention is paid to vascular wall antigens. For example, aging causes loss of elastin natural properties, and thus it becomes susceptible to deposition of calcium and elastolysis. Enhanced decomposition of insoluble elastin in the vascular wall leads to the appearance of peptides in the blood stream, whereas anti-elastin antibodies are created in response to them (40). Rabbits with experimental atherosclerosis exhibit a progressive titer increase of these antibodies, as well as abnormal accumulation of microfibrils in the elastic tissue, which is closely associated with excessive elastolysis of preformed or newly formed elastic fibers during elastic tissue remodeling. Enhanced synthesis of microfibrils may occur in response to elastolysis as a reparative phenomenon, but also represents a response of the blood vessel wall to elastolysis (33). In addition, atherosclerotic lesions accumulate ''senescent'' cells defined by markers of replicative senescence (senescence-associated b-galactosidase) and telomere shortening. Then, replicative senescence induced inflammatory gene expression (1).

Histochemical methods showed an increased non-specific esterase activity of macrophages in the arterial walls during atherogenesis induced by hypercholesterolemic diet. It has also been observed that the amount of esterase is directly proportional to the degree of saturation of the intima with lipoproteins and other macromolecules (33). Besides, it has been established that different local stimuli (immune complexes, antigens, lymphokines, bacterial components, etc.) may trigger the release of hydrolytic lysosomal enzymes into the extracellular space with autodestructive consequences. In addition, the degree of esterase activity in mononuclear cells correlates with cell viability and mitotic capacity (42).

In the vessels of obese patients, a shift of the normal prevalence of NO-mediated vasodilator tone towards an enhanced endothelin-1 (ET-1) –mediated vasoconstriction has, in fact, been observed (32). The presence of endothelial dysfunction in patients with obesity and insulin resistance (IR) was first reported by *Steinberg et al*, over a decade ago. These authors demonstrated a blunted increase of leg blood flow in response to graded intraarterial doses of the muscarinic receptor agonist methacholine in patients with elevated BMI or type 2 diabetes compared to lean controls (43). These observations have

been followed by exploration of the cellular and molecular action of insulin on the vasculature. *Quon and colleagues 2007* demonstrated that the molecular signaling pathways mediating insulin stimulation of NO production in endothelial cells are similar to signaling pathways mediating insulin activation of glucose transport in classical target tissues (i.e. the phosphatidylinositol 3-kinase /PI3K/ pathway) (44). Also, it has been shown mild elevation of fasting blood glucose after age 40 (1). The progressive glycemia of normal aging is emerging as a canonical feature of aging paralleling the increase in systolic blood pressure and atherosclerosis. It seems potentially important that mortality risk at later ages becomes increasingly sensitive to blood glucose (45).

ADIPOSE TISSUE AS AN ENDOCRINE ORGAN

For many years, adipose tissue was regarded merely as a heat insulator and a store of excess FFA that could be released when needed (46). During recent years, in fact, adipose tissue has been acknowledged as a major endocrine and paracrine organ, that produces adipokines, hormones and cytokines (32, 46, 47). These molecules contribute to the modulation of insulin activity and resistance, and metabolism of fat and glucose indirectly determining atheroslerosis (32).

Adipose tissue contains various cells, such as adipocytes, preadipocytes, vascular cells, endotheliocytes, lymphocytes and macrophages expressing CD14 receptors (47). In obesity, the increased production of inflammation mediators in the adipose tissue, liver, pancreas and skeletal muscles causes subclinical metabolic inflammation (32, 47). This inflammation affects the metabolic and secretory function of adipose tissue and plays a leading role in the development of obesity accompanying MS, diabetes mellitus and atheroslesrosis (32, 46, 47). The main source of proinflammatory mediators in this process are CD14+ cells. Furthermore, metabolic inflammation also involved cell infiltration, fibrosis development, impaired microcirculation, enhanced adipokines and proinflammatory cytokines in the visceral adipose tissue and increase of non-specific inflammatory biomarkers (CRP, fibrinogen, etc.) and leukocytes in the blood (47).

Perivascular adipose tissue (PVAT) surrounds blood vessels in changing amounts and is produced from the vascular lamina adventitia in response to circulating factors and local stimuli (46). It can be considered as a paracrine organ that transduces metabolic signals from the adipose tissue to blood vessels (48). Thus, PVAT can play an active role in regulating vascular tone and releases adipocyte-derived vascular relaxation factors into blood vessels (46, 48). Excess calories and inactivity enlarge PVAT depots with potentially unfavorable consequences and an increase in PVAT is suggested to mediate morphologic changes associated with an increse in vascular stiffness seen in obesity (46). In obesity, PVAT dysfunction triggers inflammation, oxidative stress, and hypoxic processes to promote vascular dysfunction (32).

PVAT secretes yet unidentified perivascular adipose tissue derived relaxing factor (PVADRF). In obesity, dysfunction and inflammation of adipose tissue result in impaired production of PVADRF (48). It has been shown a critical role of ROS from PVAT in the impairment of endothelium-dependent vasodilation in diet-induced obese mice (32, 48). Many adipokines with anticontractile properties, including leptin, adiponectin, angiotensin 1-7, hydrogen sulfide, visfatin and methyl palmitate have been proposed as potential candidates for PVADRF. However, none of them fully mimics the vascular effects of PVADRF and its precise identity remains to be elucidated (48).

Considering that PVAT contributes to vascular diseases, it is suggested that PVAT may be a novel target for treatment of atherosclerosis and restenosis after coronary intervention (48). Restenosis at sites of vascular injury following angioplasty is a phenomenon in which vascular smooth muscle cell (VSMC) phenotype switches to proliferation and migration as in the case in atherosclerosis (48). The local microenvironment, influenced by growth factors and inhibitors, is very important for the phenotypic conversion (32, 48). There is ample evidence that factors released from PVAT regulate VSMC proliferation and migration (32, 46, 48). It is also suggested that epicardial adipose tissue may serve as a local source of proinflammatory cytokines involved in the development of CAD. It was found in patients that there is an independent relationship between increased epicardial adipose tissue and carotid intima-media thickness (IMT) (48).

Adipokines and inflammation

The adipocytes, preadipocytes and macrophages within adipose tissue secrete a variety of hormones known as adipokines (46, 49). The list of adipokines continues to grow to hundreds of factors (32, 48). Some of these adipokines like leptin play a role in homeostasis of body weight by controlling food intake (48). High leptin concentrations correlate with adverse cardiovascular outcomes in obese patients (32). Hyperleptinemia has been shown to be an independent risk factor for CAD and a strong predictor of acute myocardial infarction and stroke (32, 50). Besides, adipose tissues expresses enzymes involved in the angiotensin system (RAS) (renin, angiotensin-converting enzyme /ACE/), as well as the nonrenin-angiotensin system (NRAS) (cathepsin D, cathepsin G, tonin, chymase) (21).

More recently, it has become clear that many adipokines are mediators in the "adipo-cardiovascular axis", the cross talk between adipose tissues, the heart and the vasculature

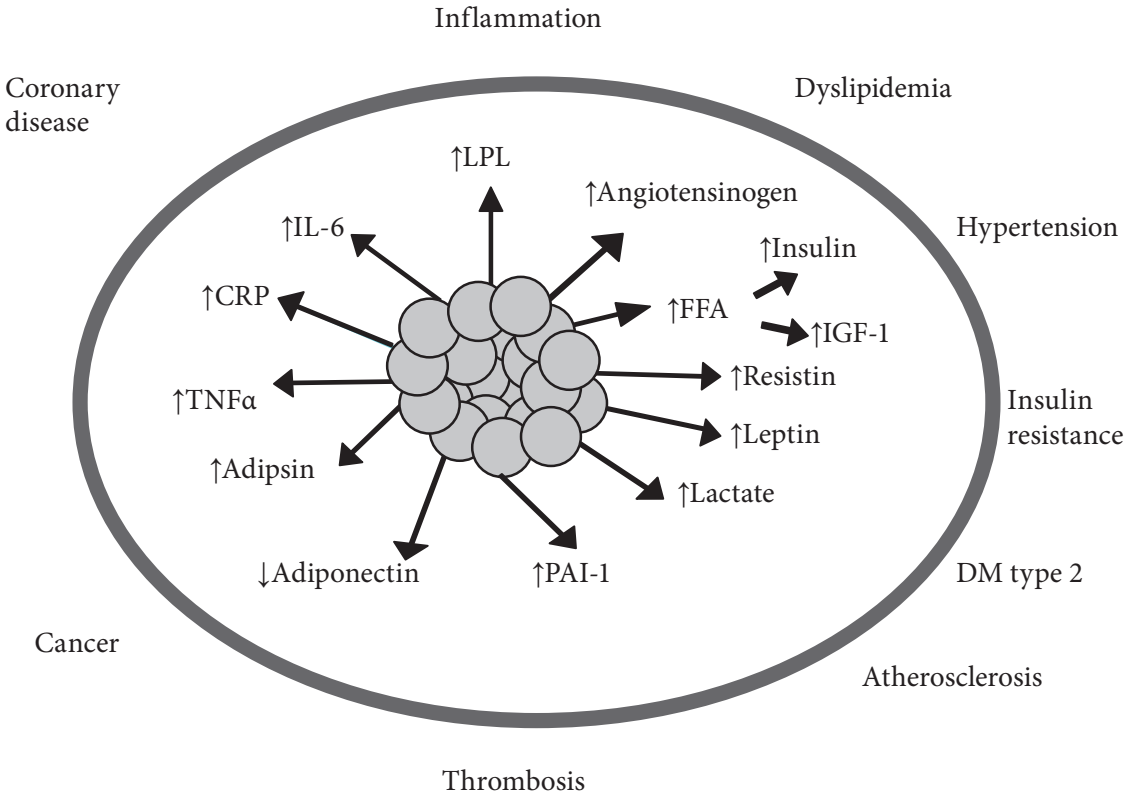
(46, 48, 49). Related to CVD one can distinct "healthy" (of which adiponectin and omentin are best characterized) and "unhealthy" adipokines. Interestingly, the "healthy" adipokines are decreased in obesity while the "unhealthy" adipokines, such as TNFa, IL-6, plasminogen activator inhibitor-1 (PAI-1), adipocyte fatty acid binding protein (A-FABP), lipocalin 2, chemerin, leptin, visfatin, vaspin, resistin are upregulated in obesity-related vascular disorders (48). The most important adipokines and their effects on vascular function is shown in Table 3. It is now evident that many of these adipokines have the ability to influence other tissues, such as liver and muscle (46). These molecules secrete into the circulation and participate in regulation of a number of chronic diseases affecting insulin sensitivity, glucose and lipid metabolism, as well as cardiovascular homeostasis (49).

Under normal conditions, the adipocyte is a site of lipid synthesis, uptake and storage (46). Secreted adipokines function as either endocrine, paracrine or autocrine mediators (32, 46, 49). Increases of adipocyte size can lead to deleterious alterations in insulin sensitivity caused by a decrease in adiponectin secretion, an increase in the release of FFA and the induction of inflammatory mediators (46, 49). Large adipocytes are more insulin-resistant and lipolytic, and release more inflammatory cytokines and less adiponectin. They are also more frequently found in individuals with obesity-related metabolic disorders (46). Enlargement of adipocytes is also associated with physical stress and increased ROS production (1, 46). These stress factors induce production of inflammatory adipokines, such as IL-6 and serum amyloid A (SAA), that are released into the circulation and mediate the recruitment of activated monocytes into adipose tissue (46, 49). In obesity, under these conditions, adipose tissues, especially activated macrophages, produce proinflammatory adipokines, such as TNFa, leptin, IL-6, monocyte chemoattractant protein-1 (MCP-1), lipocalin-2, resistin, A-FABP, PAI-1, that further encourage vascular disease (21, 46, 49). In these circumstances, production of adiponectin is markedly reduced (46-59) and inversely correlated with BMI and visceral fat (32). All of these changes have been shown to be key contributors to obesity-related vascular disease (46, 49).

Table 3. Effects of adipokines on vascular function

Adipokine	Effects on vascular function
Adipocyte fatty acid binding protein (A-FABP)	proinflammatory effect
Adiponectin	direct vasodilatory effect; ↑ VSMC proliferation and migration; ↑ vascular permeability; ↑ oxidative stress; insulin-sensitizing effect; anti-inflammatory and anti-dyslipidemic activities
Angiotensinogen	vasoconstrictor; proinflammatory effect; ↓ NO bioavailability
Apelin	proinflammatory effect
Atrial natriuretic peptide (ANP)	blood volume control
Chemerin	proinflammatory effect
C reactive protein (CRP)	proinflammatory effect; strong independent risk factor for endothelial dysfunction
Endothelin-1 (ET-1)	vasoconstriction; VSMC proliferation; cell adhesion
Free fatty acids (FFA)	↓ endothelium-dependent vasodilation
Ghrelin	vasodilation; ↑ NO production
Interleukin-1b (IL-1b)	proinflammatory effect
Interleukin-6 (IL-6)	proinflammatory effect; strong independent predictor for future cardiovascular events
Interleukin-8 (IL-8)	proinflammatory effect
Leptin	direct vasodilatory effect; ↑ VSMC proliferation and migration; ↑ vascular permeability; ↑ oxidative stress
Lipocalin-2	proinflammatory effect
Monocyte chemoattractant protein-1 (MCP-1)	proinflammatory effect
Nitric oxide (NO)	Vasodilation
Omentin	vasoprotective effect
Perivascular adipose tissue derived relaxing factor (PVADRF)	anticontractile vascular properties
Plasminogen activator inhibitor-1 (PAI-1)	↑ VSMC proliferation
Reactive oxygen species (ROS)	eNOS uncoupling; proinflammatory effect
Resistin	reduced eNOS expression; ↑ endothelial cell activity; ↑ VSMC proliferation; ↑VSMC migration
Retinol-binding protein 4 (RBP4)	proinflammatory effect
Serum amyliod A (SAA)	proinflammatory effect
Tumor necrosis factor a (TNFa)	↓ endothelium-dependent vasodilation; reduced eNOS expression; induces ET-1 and PAI-1; oxidative stress
Vaspin	proinflammatory effect
Visfatin	proinflammatory effect

Scheme 1. Inflammation and obesity-related vascular disorders



Abbreviations: CRP- C reactive protein; DM - diabetes mellitus; IGF-1 - insulin like growth factor-1; IL-6 - interleukin-6; FFA-free fatty acid; LPL-lipoprotein lipase; PAI-1 - Plasminogen activator inhibitor-1; TNFa-Tumor necrosis factor a

As in obesity, also aging is associated with altered function, size and number of adipose cells, with altered distribution of adipose tissues in the body and with hypoxia in adipose tissue, especially in the visceral depots (48).

Oxidative stress and inflammation

Endothelial dysfunction in obesity is characterised by increased generation of ROS (32, 50). This is contributed by vascular cells and inflamed hypertrophied adipocytes as a result of endoplasmic reticulum (ER) stress and mitochondrial dysfunction (8, 21, 50). Enzymes of mitochondrial electron transport chain, xanthine oxidase, cyclooxygenases, lipoxygenases, myeloperoxidases, cytochrome P450 monooxygenase, heme oxygenases, peroxidases and NAD(P)H oxidases contribute to endothelial dysfunction (50). Uncoupling of endothelial nitric oxide synthase (eNOS) is a major contributor to ROS production (32, 50). This results in decreased NO bioavailability, increased superoxide anion ($O_2^{\cdot}$) production and formation of peroxynitrite ($ONOO^-$), a key mediator of lipid peroxidation and foam cell formation in atherosclerotic lesions (50). Additionally, ROS accumulation results in activation of signalling cascades that regulate transcription factors, including nuclear factor kappa beta (NF-kb) adhesion molecules, chemotactic factors, antioxidant enzymes, and vasoactive substances promoting adhesion and migration of circulating monocytes initiating atherosclerotic lesions (39, 50). Dysregulated adipokine production leading to increased ROS generation forms a major feedback loop in initiation, maintenance and progression of endothelial dysfunction (50).

Insulin resistance and inflammation

Inflammation and IR in obese individuals are mutually amplifying processes that increase the risk of cardiovascular morbidity and mortality (32). The accumulated evidence indicates that IR is a key pathogenic factor for MS (59). Namely, it is generally believed that elevated blood pressure, dyslipidemia and impaired glucose tolerance are caused by IR (24, 25, 27, 59).

IR is often associated with increased adipose tissue mass (59). Proinflammatory cytokines produced by adipocytes contribute, at least in part, to IR by interfering with normal insulin receptor intracellular signaling (32). On the other hand, obesity-related IR is well-known to promote inflammation through diverse mechanisms including oxidative stress, stimulation of proinflammatory adipokines, AGEs, and FFAs (32). Dysfunctional adipose tissue with low grade, chronic and systemic inflammation links the metabolic and vascular pathogenesis including dyslipidemia, low grade inflammation and IR and is a hallmark of disorders such as type 2 diabetes and CVD (46). However, lifestyle factors and, to a lesser degree, genetic factors, are also involved (32, 46).

Lipid accumulation in liver and muscle is an early hallmark of type 2 diabetes (11, 12, 46). In the pancreas, lipid accumulation has been shown to precede suppressed glucose-mediated insulin production (46). In the lipid-overloaded heart, metabolic dysregulation may induce IR resulting in impaired glucose oxidation, and, ultimately, heart failure (6, 46).

Large adipocytes are more frequently found in subjects with impaired glucose tolerance and type 2 diabetes than those with a similar degree of adiposity but with normal glucose tolerance, and impaired adipocyte differentiation appears to be one of the most important factors in the progression of type 2 diabetes (46). Insulin has several functions, including the transport of nutrients into cells, the regulation of gene expression and energy homeostasis. It acts on a number of target tissues and through many different intracellular signaling cascades (8, 10, 14). Elevated levels of intracellular FFAs can blunt the response to insulin and subsequent metabolic effects (32, 46).

Insulin receptor substrate-1 (IRS-1) is a key molecule in the insulin signaling pathway and failure to activate IRS-1 leads to systemic IR (46). Inhibitory phosphorylation of IRS-1 can be induced through inflammatory agents, such as TNFa and IL-6, but also through activation of receptors, such as the Toll-like receptors (TLR), or intracellular molecules such as lipids and ROS (27, 46). Activation of the TNFa and IL-6 receptors induces activation of important activators of inflammation i.e. IkB kinase (IKKb) and Janus kinase (JNK) (46). JNK is also activated by FFAs and ER stress, factors that are associated with obesity-induced activity (25, 27, 46). IKKb does not phosphorylate IRS-1, but causes IR through activation of NFkB (25). Supressor of cytokine signalling (SOCS) inhibits insulin actions on IRS-1, either by interfering with the tyrosine phosphorylation, or by targeting IRS-1 for proteosomal degradation (46).

The consequences of decreased insulin production as a result of ectopic lipid accumulation in the pancreas combined with a diminished activation of the insulin receptor in adipocytes results in an impairment of insulin-stimulated glucose transport, a reduced anti-lipolytic effect, an increase in the amount of FFA released, impaired preadipocyte differentiation and a decrease in lipoprotein lipase (LPL) production and activity (46). These effects will lead to the development of IR, type 2 diabetes and CVD (46, 51).

An increase in the amount of AGEs also contribute to the development of vascular complications in diabetes, inducing endothelial dysfunction (16, 17, 51). Several mechanisms by which this heterogeneous group of compounds formed by nonenzymatic glycation of proteins and lipids lead to endothelial dysfunction have been proposed, such as the accumulation of AGEs in the extracellular matrix, the binding of circulating AGEs to the endothelial surface receptor for AGEs (RAGE) with subsequent generation of ROS, the cytokine release and the expression of cell adhesion molecules (51).

NAFLD AND ADIPOSE TISSUE INFLAMMATION

The liver is an organ that is vulnerable to ectopic fat accumulation (60). Currently, the incidence of nonalcoholic fatty liver disease (NAFLD) mirrors the prevalence of obesity and MS, and NAFLD is now one of the most common causes of chronic liver disease worldwide (61). Notably, NAFLD is not a single disease entity, but describes a spectrum of liver conditions. The disorder ranges from simple fatty liver (steatosis) to more severe steatosis coupled with marked inflammation termed nonalcoholic statohepatitis (NASH), which can progres to fibrosis, and subsequently to liver cirrhosis, liver failure and hepatocellular carcinoma (62).

NAFLD is now considered as a hepatic manifestation of MS (60-62). In support of this, recent studies have shown that severe NAFLD is linked to an incressed risk of CVD (25, 27, 60, 62). These studies suggest that NAFLD may be actively involved in the pathogenesis of CVD, potentially through the increased release of proatherogenic factors from the liver (CRP, fibrinogen, PAI-1 and other inflammatory cytokines). Alternatively, NAFLD is involved in in whole-body IR and dyslipidemia. For example, once significant hepatic steatosis occurs, the liver becomes insulin resistant and overproduces both glucose and VLDL, which in turn leads to hyperglycemia, hypertriglyceridemia and low concentration of high density lipoproteins (HDL) (62). However, whether IR precedes ectopic fat deposition or whether fat accumulation is a consequence of IR remains an unanswered question (64).

As previously described, ectopic fat is an important source of inflammatory mediators, cytokines and adipokines. It is possible that adipose tissue inflammation plays a role in the pathogenesis of NAFLD (63). Indeed, analysis of adipose tissue from subjects with severe liver steatosis has suggested that inflamed adipose tissue characterises people with a high liver fat content (65). In mice, the overexpression of an inflammatory marker in adipose tissue, macrophage chemotactic protein-1 (MCP-1), is thought to lead to macrophage infiltration and hepatic steatosis (66). However, it is also possible that hepatic inflammation may precede that of other insulin-sensitive tissues, as the hepatic activation of NFkB via overexpression of IKKb can induce IR in the liver and muscle in addition to an increase in signs of systemic inflammation (IL-6) (63). In response to these findings, one can draw similarities between hepatic fat and more traditional sites of proinflammatory adiposopathic ectopic fat, predominantly influenced by a high

fat diet (67). Therefore, liver with NAFLD may play an even larger role in the whole body inflammatory state, because the liver itself is in an advanced state of inflammation (68, 69).

INFLAMMATION, OBESITY-RELATED VASCULAR DYSFUNCTIONS AND AGING PROCESS

Cardiovascular events, diabetes mellitus resulting from the MS as well as cancer are the common cause od death of aging humans (27, 28). Why is it so? As it is previously described, advancing age affects all levels of patgogenic components of the MS (27-29). With aging we assist to a change in the body composition characterised by the redistribution of the body composition in favour of the adipose tissue. The increase in the adipose tissue is especially marked centrally, as well as in muscle and liver. In the mean time the lean body mass is also decreasing, which favours the IR in the muscle (27). In addition, the aging process is associated with a low grade inflammation due to the deregulated functioning of the innate immune system over adaptive immune system resulting from chronic antigenic stimulation of all types including infections and nutrition (1, 27, 70, 71). This results in the increase in circulating levels of FFA and proinflammatory cytokines enforcing the already existing IR (27). Thus, the better understanding of the interplay between the metabolic response and immunosenescence could lead to important understanding of both processed during aging.

Aging is also associated with a change in the hormones implicated in metabolism including insulin like growth factor-1 (IGF-1), the growth hormone and insulin (1, 27, 72-74). IGF-1 recently has become a major determinant in nematode and fly longevity (27). Evidence suggests that disruption in IGF-1 signalling uniformly extends lifespan in animal species (1, 27). Of course, no direct conclusion can be drawn for human longevity (27). However, the decrease, as well as the increase IGF-1 levels were related to various diseases (27, 74). Insulin sensitivity declines with age and is associated with increased morbidity and mortality due to atherosclerosis, CVD, obesity and diabetes, all related to dysregulation of the aging immune system (immunosenescence) (27, 31, 77), as well as to dementia (20). Studies in healthy centenarians show enhanced insulin sensitivity demonstrating an important role of healthy insulin signalling for long life (27). How exactly it could happen is still to be discovered. Probably the newly discovered SIRT gene family, actually seven members could play an important role (1, 27). Nevertheless, vigorous prevention and/or treatment of IR and components of the MS could have important implications for human longevity (27).

Caloric restriction and inflammation

Many observational and experimental studies have considered that caloric restriction may be associated with life prolongation, possibly through an improvement of the cell redox balance (78). Also, increase degeneration of mitochondrial ROS and oxidative damage seem to be differently induced by nutritional perturbation and state (31, 78, 79). In animal experiments, hypocaloric diet and antioxidant supplementation were associated with improvement of some tissue functions and redox states that, conversely, were oxidatively depressed in aged control animals (78). A key event associated with diet restriction is the activation of a class of genes belonging to the SIRT family, which is involved in cell maturation and apoptotic processes (1, 27, 78). Recently, it is shown that resveratrol, an antioxidant poliphenol of red wine, was able to activate these genes by mimicking the effect of diet restriction (31, 78). Successively, it is reported that high dose of resveratrol was able to contrast the development of CVD and diabetes in mice fed with hypercaloric diet, suggesting a role for oxidative stress in systemic inflammation and damages in conditions stimulating the MS (31, 78).

Diet has major systemic influences on inflammation through the levels of energy intake, energy storage in fat depots, and ingested AGEs produced during cooking (1). As a general principle, innate immune responses are regulated by the energy available (1, 3, 70). Caloric restriction, besides limiting the febrile response, attenuates other acute phase responses (1). A systemic mechanism in caloric restriction may be elevation of corticosteroids, which is a broad gluconeogenic homeostatic response to partial starvation to maintain sufficient levels of blood glucose (1, 2). Lowering of blood glucose by caloric restriction attenuated production of AGEs, that further kindling inflammatory process (1). Besides, AGEs can act directly on pancreatic cells to impair insulin secretion through induction of iNOS (1). The oxidative load also is diminished by caloric restriction in most tissues (1, 27, 31, 67, 78, 80-82).

Gene expression profiling studies consistently show that caloric restriction attenuates the increased expression of cytokine and complement factor genes during aging in brain, heart, and liver (1, 83, 84). Caloric restriction also attenuates atherosclerosis, cancer and Alzheimer' disease in rodent models (1, 27, 78). In moderately obese patients, diet restriction lowered blood CRP and IL-6, with correspondingly lower incidence of cardiovascular events (1).

CONCLUSION

The pathogenesis of obesity-related vascular disorders has not been fully elucidated. The fundamental role of inflammation in aging process is now widely recognized,

particularly for atherosclerotic disease which begins before birth. The strong age trends for elevated blood glucose and glycated proteins during starting midlife is hypothesized to be a fundamental driver of vascular disease and the acceleration of risk for cerebrovascular events. Obesity and MS are important risk factors for metabolic and CVD. Despite a well-known genetic component, this risk appears to originate from several abnormalities in adipose tissue function associated with a chronic inflammatory state. These conditions disrupt vascular homeostasis by causing an imbalance between the NO pathway and the ET-1 system, with impaired insulin-stimulated endothelium-dependent vasodilation.

Many research efforts are still required to unravel the complex relation between adipose tissue and CVD and the potential role of adipokines as biomarkers. A hope remains that future research on the role of these biological active molecules in the pathogenesis of obesity-related vascular disfunctions will shed light on yet unknown potential therapeutic modalities.

Acknowledgements

This work was supported by the Ministry of Education, Science and Technological Development of Republic of Serbia, Grant No. 175015.

REFERENCES

1. Finch CE. Inflammation in aging processes: an integrative and ecological perspective. In: Masoro E, Austad S, editors. Handbook of the biology of aging. San Diego:Academic Press; 2010. p. 1-45.
2. Finch CE. Evolution in health and medicine Sackler colloquium: Evolution of the human lifespan and diseases of aging: roles of infection, inflammation, and nutrition. Proc Natl Acad Sci U S A 2010;107:1718-24.
3. Finch CE. The biology of human longevity: inflammation, nutrition, and aging in the evolution of lifespans. 1st edition. San Diego: Academic Press; 2007.
4. Mathieu P, Battista D, Depino A, et al. The more you have, the less you get: the functional role of inflammation on neuronal differentiation of endogenous and transplanted neural stem cells in the adult brain. J Neurochem 2010;112:1368-85.
5. Abarbanell AM, Coffey AC, Fehrenbacher JW, et al. Proinflammatory cytokine effects on mesenchymal stem cell therapy for the ischemic heart. Ann Thorac Surg 2009;88:1036-43.
6. Herrmann JL, Markel TA, Abarbanell AM, et al. Proinflammatory stem cell signaling in cardiac ischemia. Antioxid Redox Signal 2009;11:1883-96.
7. Korner J, Woods SC, Woodworth KA. Regulation of energy homeostasis and health consequences in obesity. Am J Med 2009;122:S12-8.
8. Lee DE, Kehlenbrink S, Lee H, et al. Getting the message across: mechanisms of physiological cross talk by adipose tissue. Am J Physiol Endocrinol Metab 2009;296:E1210-29.
9. Redinger RN. Fat storage and the biology of energy expenditure. Transl Res 2009;154:52-60.
10. Khaodhiar L, Ling PR, Blackburn GL, et al. Serum levels of interleukin-6 and C-reactive protein correlate with body mass index across the broad range of obesity. JPEN J Parenter Enteral Nutr 2004;28:410-5.
11. Maury E, Brichard SM. Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. Mol Cell Endocrinol 2010;314:1-16.
12. Fontana L, Eagon JC, Trujillo ME, et al. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. Diabetes 2007;56:1010-3.
13. Minamino T, Orimo M, Shimizu I, et al. A crucial role for adipose tissue p53 in the regulation of insulin resistance. Nat Med 2009;15:1082-7.
14. Hevener AL, Febbraio MA; Stock Conference Working Group. The 2009 stock conference report: inflammation, obesity and metabolic disease. Obes Rev 2010;11:635-44.
15. Cai W, He JC, Zhu L, et al. AGE-receptor-1 counteracts cellular oxidant stress induced by AGEs via negative regulation of p66shc-dependent FKHRL1 phosphorylation. Am J Physiol Cell Physiol 2008;294:C145-52.
16. Lin L, Park S, Lakatta EG. RAGE signaling in inflammation and arterial aging. Front Biosci (Landmark Ed) 2009;14:1403-13.
17. Herold K, Moser B, Chen Y, et al. Receptor for advanced glycation end products (RAGE) in a dash to the rescue: inflammatory signals gone awry in the primal response to stress. J Leukoc Biol 2007;82:204-12.
18. Gao L, Mann GE. Vascular NAD(P)H oxidase activation in diabetes: a double-edged sword in redox signalling. Cardiovasc Res 2009;82:9-20.
19. Chou MY, Hartvigsen K, Hansen LF, et al. Oxidation-specific epitopes are important targets of innate immunity. J Intern Med 2008;263:479-88.
20. Nguyen JC, Killcross AS, Jenkins TA. Obesity and cognitive decline: role of inflammation and vascular changes. Front Neurosci 2014;8:375.
21. Wang Z, Nakayama T. Inflammation, a link between obesity and cardiovascular disease. Mediators Inflamm 2010;2010:535918.
22. Li Z, Bowerman S, Heber D. Health ramifications of the obesity epidemic. Surg Clin North Am 2005;85:681-701.
23. Olshansky SJ. Projecting the future of U.S. health and longevity. Health Aff (Millwood). 2005;24:W5R86-9.
24. Grundy SM. Obesity, metabolic syndrome, and cardiovascular disease. J Clin Endocrinol Metab 2004;89:2595-600.
25. Haslam DW, James WP. Obesity. Lancet 2005;366:1197-209.
26. Pignone M, Salazar R. Disease prevention and health promotion. In: McPhee SJ, Papadakis MA, editors. Current medical diagnosis and treatment. New York:Mc Graw Hill; 2011. p. 1-21.
27. Fulop T, Tessier D, Carpentier A. The metabolic syndrome. Pathol Biol (Paris) 2006;54:375-86.
28. Bechtold M, Palmer J, Valtos J, et al. Metabolic syndrome in the elderly. Curr Diab Rep 2006;6:64-71.
29. Morley JE. The metabolic syndrome and aging. J Gerontol A Biol Sci Med Sci 2004;59:139-42.
30. Caglayan E, Blaschke F, Takata Y, et al. Metabolic syndrome-interdependence of the cardiovascular and metabolic pathways. Curr Opin Pharmacol 2005;5:135-42.
31. Mohamed S. Functional foods against metabolic syndrome (obesity, diabetes, hypertension and dyslipidemia) and cardiovascular disease. Trend Food Sci Technol 2014;35:114-128.
32. Iantorno M, Campia U, Di Daniele N, et al. Obesity, inflammation and endothelial dysfunction. J Biol Regul Homeost Agents 2014;28:169-76.
33. Vučević D, Radosavljević T, Djordjević D, et al. The relationship between atherosclerosis and pulmonary emphysema. Med Pregl 2014;67:231-8.
34. Vučević D, Milovanović I, Mladenović I, et al. The effect of tocopherol on serum lipid profile in pulmonary emphysema induced by hyperholesterolemic diet. Acta Vet 2007;57:303-20.
35. Vučević D, Pešić BČ, Djarmati D, et al. Effect of tocopherol on experimental emphysema in rabbits. Period Biolog 2004;106:411-16.
36. Vučević D, Pešić BČ, Djarmati D, et al. The effect of tocopherol on serum iron content in experimental atherosclerosis. Acta Vet 2005;55:131-45.
37. Vučević D, Radosavljević T, Mladenović D, et al. Iron as an agent of oxidative injury in experimental atherosclerosis. Acta Vet 2011;61:631-41.
38. Frostegård J. Immunity, atherosclerosis and cardiovascular disease. BMC Med 2013;11:117-129.
39. Valko M, Leibfritz D, Moncol J, et al. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007;39:44-84.

40. Frostegård J. Immune mechanisms in atherosclerosis, especially in diabetes type 2. Front Endocrinol (Lausanne) 2013;4:162-172.
41. Song Z, Jin R, Yu S, et al. Crucial role of CD40 signaling in vascular wall cells in neointimal formation and vascular remodeling after vascular interventions.Arterioscler Thromb Vasc Biol 2012;32:50-64.
42. Lahoute C, Herbin O, Mallat Z, et al. Adaptive immunity in atherosclerosis: mechanisms and future therapeutic targets. Nat Rev Cardiol 2011;8:348-58.
43. Steinberg HO, Chaker H, Leaming R, et al. Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. J Clin Invest 1996;97:2601-10.
44. Muniyappa R, Montagnani M, Koh KK, et al. Cardiovascular actions of insulin. Endocr Rev 2007;28:463-91.
45. Yashin AI, Ukraintseva SV, Arbeev KG, et al. Maintaining physiological state for exceptional survival: What is the normal level of blood glucose and does it change with age? Mech Ageing Dev 2009;130:611-8.
46. Gustafson B.Adipose tissue, inflammation and atherosclerosis. J Atheroscler Thromb 2010;17:332-41.
47. Litvinova L, Atochin D, Vasilenko M, et al. Role of adiponectin and proinflammatory gene expression in adipose tissue chronic inflammation in women with metabolic syndrome. Diabetol Metab Syndr 2014;6:137 doi:10.1186/1758-5996-6-137
48. Van de Voorde J, Pauwels B, Boydens C, et al. Adipocytokines in relation to cardiovascular disease. Metabolism 2013;62:1513-21.
49. Ebrahimi-Mamaeghani M, Mohammadi S, Arefhosseini SR, et al. Adiponectin as a potential biomarker of vascular disease. Vasc Health Risk Manag 2015;11:55-70.
50. Adya R, Tan BK, Randeva HS. Differential effects of leptin and adiponectin in endothelial angiogenesis. J Diabetes Res 2015;2015:648239.
51. Del Turco S, Navarra T, Gastaldelli A, et al. Protective role of adiponectin on endothelial dysfunction induced by AGEs: a clinical and experimental approach. Microvasc Res 2011;82:73-6.
52. Bachmayer C, Kemmer A, Ehrmann N, et al. Adipokines and endothelial dysfunction in obesity WHO°III. Microvasc Res 2013;89:129-33.
53. Kizer JR. Adiponectin, cardiovascular disease, and mortality: parsing the dual prognostic implications of a complex adipokine. Metabolism 2014;63:1079-83.
54. Nigro E, Scudiero O, Monaco ML, et al. New insight into adiponectin role in obesity and obesity-related diseases. Biomed Res Int 2014;2014:658913.
55. Chang X, Jiao Y, Lu J, et al. Adiponectin and visfatin may serve as diagnosis markers for metabolic syndrome in Uygur population. Int J Clin Exp Med 2014;7:4322-6.
56. Funahashi T, Matsuzawa Y. Adiponectin and the cardiometabolic syndrome: an epidemiological perspective. Best Pract Res Clin Endocrinol Metab 2014;28:93-106.
57. Dessein PH, Tsang L, Solomon A, et al. Adiponectin and atherosclerosis in rheumatoid arthritis. Mediators Inflamm 2014;2014:358949.
58. Lee S, Kwak HB. Role of adiponectin in metabolic and cardiovascular disease. J Exerc Rehabil 2014;10:54-9.
59. Ding Y, Li S, Ma RL, et al. Association of homeostasis model assessment of insulin resistance, adiponectin, and low-grade inflammation with the course of the metabolic syndrome. Clin Biochem 2015;48:503-7.
60. Snel M, Jonker JT, Schoones J, et al. Ectopic fat and insulin resistance: pathophysiology and effect of diet and lifestyle interventions. Int J Endocrinol 2012;2012:983814.
61. Cusi K. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications. Gastroenterology. 2012;142:711-25.
62. Gaggini M, Morelli M, Buzzigoli E, et al. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. Nutrients 2013;5:1544-60.
63. Leamy AK, Egnatchik RA, Young JD. Molecular mechanisms and the role of saturated fatty acids in the progression of non-alcoholic fatty liver disease. Prog Lipid Res 2013;52:165-74.
64. Cerović I, Mladenović D, Ješić R, et al. Alcoholic liver disease/nonalcoholic fatty liver disease index: distinguishing alcoholic from nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol 2013;25:899-904.
65. Friedman LS. Liver, biliary tract and pancreas disorders. In: Papadakis MA, McPhee SJ, editors. Current medical diagnosis and treatment. New York:Mc Graw Hill; 2016. p. 663-720.
66. Chavez-Tapia NC, Rosso N, Tiribelli C. Effect of intracellular lipid accumulation in a new model of non-alcoholic fatty liver disease. BMC Gastroenterol 2012;12:20.
67. Mladenović D, Ninković M, Aleksić V, et al. The effect of calorie restriction on acute ethanol-induced oxidative and nitrosative liver injury in rats. Environ Toxicol Pharmacol 2013;36:296-302.
68. Jorgačević B, Mladenović D, Ninković M, et al. Dynamics of oxidative/nitrosative stress in mice with methionine-choline-deficient diet-induced nonalcoholic fatty liver disease. Hum Exp Toxicol 2014;33:701-9.
69. Stanković MN, Mladenović DR, Duričić I, et al. Time-dependent changes and association between liver free fatty acids, serum lipid profile and histological features in mice model of nonalcoholic fatty liver disease. Arch Med Res 2014;45:116-24.
70. Osborn O, Olefsky JM. The cellular and signaling networks linking the immune system and metabolism in disease. Nat Med 2012;18:363-74.
71. Juonala M, Magnussen CG, Berenson GS, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N Engl J Med 2011;365:1876-85.
72. Radosavljević T, Todorović V, Šikić B, et al. Insulin-like growth factor-I in rats with portcaval shunting. Period Biolog 2004;106:403-10.
73. Radosavljević T, Todorović V, Nikolić I, et al. Gastrin (G) and enterochromaffin-like (ELC) cells in the stomach portcaval-shunted rats. A radioimmunological, immunocitochemical and ultrasound study. Acta Veterin 2005;55:23-30.
74. Westley RL, May FE. A twenty-first century cancer epidemic caused by obesity: the involvement of insulin, diabetes, and insulin-like growth factors. Int J Endocrinol 2013;2013:632461.
75. Harris MF. The metabolic syndrome. Aust Fam Physician 2013;42:524-7.
76. Murphy R, Carroll RW, Krebs JD. Pathogenesis of the metabolic syndrome: insights from monogenic disorders. Mediators Inflamm 2013;2013:920214.
77. Qatanani M, Tan Y, Dobrin R, et al. Inverse regulation of inflammation and mitochondrial function in adipose tissue defines extreme insulin sensitivity in morbidly obese patients. Diabetes 2013;62:855-63.
78. Grattagliano I, Palmieri VO, Portincasa P, et al. Oxidative stress-induced risk factors associated with the metabolic syndrome: a unifying hypothesis. J Nutr Biochem 2008;19:491-504.
79. Ma ZA, Zhao Z, Turk J. Mitochondrial dysfunction and β-cell failure in type 2 diabetes mellitus. Exp Diabetes Res 2012;2012:703538.
80. Vučević D, Mladenović D, Ninković M, et al. Influence of aging on ethanol-induced oxidative stress in digestive tract of rats. Hum Exp Toxicol 2013;32:698-705.
81. Vučević D, Mladenović D, Ninković M, et al. The effects of caloric restriction against ethanol-induced oxidative and nitrosative cardiotoxicity and plasma lipids in rats. Exp Biol Med (Maywood) 2013;238:1396-405.
82. Stanković M, Mladenović D, Ninković M, et al. Effects of caloric restriction on oxidative stress parameters. Gen Physiol Biophys 2013;32:277-83.
83. Young LH. Diet-induced obesity obstructs insulin signaling in the heart. Am J Physiol Heart Circ Physiol 2010;298:H306-7.
84. Jornayvaz FR, Shulman GI. Diacylglycerol activation of protein kinase Cε and hepatic insulin resistance. Cell Metab 2012;15:574-84.

INDEKS AUTORA

Aleksandar Jakovljević 32
Biljana Putnikovic 1
Bojan Jorgačević 32
Bozidarka Zaric 1
Danijela Vučević 32
Darija Kisić Tepavčević 14
Đorđe Radak 32
Dragana Stanić 7,20
Dragica Kosi 25
Drago Đorđević 32
Esma Isenovic 1
Ivana Resanovic 1
Jelena Bokun 7
Maja Miletić 32
Marina Nikitović 7, 20
Milena Vesković 32
Nataša Maksimović 14
Nikolina Banjanin 29
Pejka Kovacevic 1
Sasa Radenkovic 1
Zoran Gluvic 1

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Izdavač i vlasnik: MEDICINSKI FAKULTET UNIVERZITETA U BEOGRADU

Uredništvo i administracija: 11105 Beograd, Dr Subotića br. 8, soba 311

Realizacija: SPRINT, BEOGRAD

Tiraž: 300 primeraka