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DIRECTIONS IN DIAGNOSIS, HEALTH RELATED QUALITY OF LIFE AND THERAPY OF PROSTATE CANCER – CONTROVERSIES IN URO-ONCOLOGY

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Currently, it is recommended that prostate cancer be detected by digital rectal palpation and prostate specific antigen (PSA) elevation. TRUS coupled with ultrasound-guided biopsies might become the most appealing staging technique for early diagnosed prostate cancer. To promote earlier diagnosis, better PSA thresholds need to be defined, with a clear free-PSA threshold. This could be complemented by the use of nomograms and, in suspected cases, repeated biopsies, TRUS, bone scans and new imaging techniques. Deferred therapy by means of active observation and alertness to start therapy when signs of rapid progression occur may therefore be an alternative to active therapy in patients with low-risk localized prostate cancer with life expectancy of 10 years or less. Radical prostatectomy was more effective than watchful waiting in terms of cancer-specific survival benefit, when compared in a prospective randomized trial. Neoadjuvant hormonal therapy has a nonsignificant impact on overall and progression free survival. In Europe, the focus is on biochemical recurrence after curative treatment (nerve sparing radical prostatectomy and/or radiotherapy in low-, intermediate- and high-risk patients with 72-78 Gy. In metastatic disease, adjuvant androgen deprivation is the treatment of choice. These are patients that cannot be cured. Identification of intracellular androgen synthesis by prostate cancer cells has led to identification of new targets, several novel strategies, third-generation drugs, inhibitors of androgen synthesis, more potent androgen receptor antagonists. Castration-resistant prostate cancer remains dependent on androgens and signaling through androgen receptor. Substantial pain reduction, improvement in PSA response and quality of life often make chemotherapy with docetaxel for hormone refractory prostate cancer better choice than simple pain and complication treatment. The main features of each condition and its management are summarized.

Key words: **prostate cancer, treatment, surgery, castration, hormonal treatment, chemotherapy, radiotherapy, quality of life**

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INTRODUCTION

We would like to address reader's attention to the paper that defines in most cases the point of view of the European Association of Urology (EAU) (1). We tried to present an update of the most recent literature that appeared in the last few years and hope to provide the reader with a complex view of this complex field of medical science. It was done in an effort to address clinical challenges that confront the practicing urologist in the field of prostate cancer.

EPIDEMIOLOGY

According to Cooperberg *et al.* (2) and Corica and Bostwick (3), the incidence of prostate cancer increases with population age, reaching maximum prevalence of 33% in those aged >70 years (4). Prostate cancer is now the most commonly diagnosed malignancy in men, accounting for approximately 2.6 million of cancers newly diagnosed in Europe annually. This disease accounts for 11% of all male cancers in Europe (5) and for 9% of all cancer deaths in the European Union (6).

RISK OF PROSTATE CANCER AND ETIOLOGY

It has been observed for decades that more than one member of the same family can be affected by prostate cancer. Genetic basis and racial differences for this disease are well established, but epidemiological significance of familial factors is difficult to demonstrate (7). Some environmental factor cannot be ruled out either, insofar as many members of the same family may be exposed to the same risk factor, not recognizable in most cases. There was a higher risk with the increasing number of family members affected (8). Men with 2 or 3 first-degree relatives with prostate cancer had a 5- and 11-fold greater risk of developing the disease, respectively (9). Carter *et al*. (10) report that inherited prostate cancer should be suspected in men with the disease onset before 55 years of age or in males with 2 or more affected relatives.

CLASSIFICATION

The International Union Against Cancer (UICC) 2002 Tumor, Node, Metastases (TNM) classification is used for staging (11). There are several systems of tumor grade classification. Gleason's system is most commonly used for grading of prostate adenocarcinoma (12). Gleason grading system is based on the analysis of various microscopic criteria of the tumor at low power magnification, which are divided into 5 appearances scored from 1 to 5. As the tumor does not have a uniform appearance, this system takes into account the two most extensive appearances in terms of area (primary and secondary patterns). If the tumor contains smaller areas of other appearances, they are not taken into account in the final histological grade, even if one of them corresponds to a more poorly differentiated pattern. The histological grade is the sum of the two histological patterns defined or twice the score of the simple pattern detected. It is therefore scored from 2 to 10. To be counted, a pattern (grade) needs to occupy more than 5% of the biopsy (core or operative specimen). Gleason's system results in a histological score that is closely correlated with patient survival (13).

SCREENING AND EARLY DETECTION

The demand for a routine preventive cancer checkup is based on the oncologic principle that all diseases have a better chance of cure if they are detected and thus treated at an early stage (14). Population or mass screening is defined as the examination of asymptomatic male (at risk). In addition, the principle also implies that screening currently includes a study and is initiated by a screener. Contrary to this, early detection represents individual case findings. It is initiated by the patient and/or his physician.

Reduction in mortality from prostate carcinoma varies greatly worldwide across industrialized countries (15). Screening for prostate cancer is based on the assumption that it is a relevant public health concern. Prospective, preferably population-based, randomized studies are still required. Two prospective studies have been completed: the Prostate, Lung, Colorectal and Ovary (PLCO) trial in the USA and the European Randomized Screening for Prostate Cancer (ERSPC) in Europe. The PLCO investigators found a higher incidence of prostate carcinoma in the screening group than in control group, but with the same rates of death from the disease (16). The ERSPC investigators have reported a higher incidence of prostate carcinoma in the prostate specific antigen (PSA) based screening group than in the non-screening group; however, men undergoing screening had a lower rate of death from prostate carcinoma (17).

Thus, it appears that PSA test could be recommended for prostate carcinoma screening at the present. The patient should first be informed about the potential harms and benefits of screening. Undoubtedly, there are as many prostate cancers now detected by PSA elevations without digital rectal abnormalities as there are cancers detected through positive digital rectal examination (18).

DIAGNOSIS AND STAGING

Currently, it is recommended that a cancer must be detected by digital rectal examination (DRE) and PSA elevation (19-21). Transrectal ultrasonography (TRUS) coupled with ultrasound (US)-guided biopsies might become the most appealing staging technique for early diagnosed prostate cancer. To better characterize cancers by biopsy, investigators have explored enhanced image guidance with magnetic resonance imaging (MRI); it may supplement but cannot replace systematic sampling techniques.

Thompson *et al*. (22) observed that many men may harbor prostate cancer despite low PSA values, as underscored by recent results from a US prevention study. An important question concerning clinical practice is that the free-to-total PSA ratio <20% and PSA velocity >0.75 ng/mL/year have been accepted as valid parameters that are associated with an increased risk of prostate carcinoma (23). Up to now, 12,078 men undergoing prostate biopsy were followed-up in a recent retrospective study. Threshold values of PSA

and PSA velocity were identified to improve assessment of prostate carcinoma risk in men beyond age 50 (24). Extensive studies showed the prevalence of prostate carcinoma to be 4.4% and 14.2% in men aged <50 and >50, respectively. According to these data, a PSA threshold level >2.5 ng/mL and PSA velocity threshold level >0.60 ng/mL/year seem to be appropriate for clinical practice.

The US-guided transrectal 18G core biopsy has been generally accepted and has become a standard method to obtain prostate tissue for histopathologic examination (25). According to several studies, it is possible to reach a higher cancer detection rate in an extended 21-sample biopsy compared with the standard sextant technique (26,27). In most of the studies, it was clearly shown that the transition zone should not be the target area for the first set of prostate biopsies. An overall accuracy of 2% cancer detection rate is to be expected (28).

In the experience of the authors, if the first set of biopsies is negative, repeat biopsies can be recommended. The second set of biopsies exhibit a detection rate of 10%-35% (29). It is known that high-grade prostatic intraepithelial neoplasia (HGPIN) will suggest carcinoma in as many as 50%-100% of prostates. Clinical follow up and repeat biopsies are indicated (30).

PRIMARY TREATMENT OF PROSTATE CANCER, EARLY PROSTATE CANCER MANAGEMENT, SURGERY, RADIATION OR ACTIVE SURVEILLANCE

Different urologists have their own special methods for dealing with presumed localized prostate cancer (radical prostatectomy). These additional methods include watchful waiting (31), and external and/or interstitial radiation. An important thing is the absence of metastases. When they are absent, any treatment that completely removes or destroys the primary growth will result in cure, and when metastases are present, none is likely to do so. When making such decisions, many physicians rely on nomograms based on preoperative biochemical markers and biopsies (32).

WATCHFUL WAITING AND ACTIVE SURVEILLANCE

The efficacy of different types of treatment for localized prostate cancer has come under question. While radical prostatectomy and radiotherapy have been associated with low progression rates and high survival figures, it is well known that in many patients the cause of death is not prostate cancer. There is therefore a renewed interest in studying the natural history of this disease to better appreciate to what extent active forms of treatment may alter the outcome (33,34).

Deferred therapy by means of active observation (35) and alertness to start therapy when signs of rapid progression occur (36) may therefore be an alternative to active therapy in patients with low-risk localized prostate cancer and life expectancy of 10 years or less (37). Chodak *et al.* (33) and Albertsen *et al.* (34) observed 80%-90% cancer specific survival with deferred therapy after 20-year follow-up. The excellent article by Chodak *et al.* (33) describes the outcome in stage T1a patients, with cancer-specific 10-year survival rate of 90%.

Classification of Gleason score, stage and PSA level are mandatory to assess the risk of tumor progression and ultimately death from prostate cancer. Results observed in a series of patients showed that patients with a PSA <10 ng/mL, biopsy Gleason score ≤6, stage cT1c-cT2a, and life expectancy <10 years should be managed expectantly.

The established therapeutic approaches for clinically nonsignificant prostate cancer include watchful waiting and active surveillance. The optimal treatment strategy for a patient should provide long-term disease control with minimal treatment-related morbidity and maximal preservation of the quality of life.

Traditional conservative symptomatic management with palliative intention, especially in elderly patients with meaningful comorbidity, treatment options are hormone therapy, palliative transurethral resection (TUR-P), and palliative radiotherapy of bone metastases.

In a pivot trial of radical prostatectomy *versus* observation watchful waiting (WW), investigators report that some populations do not profit from radical prostatectomy, as it could be an overtreatment (38). Other investigators (SPCG-4-study) have reported reduction of mortality associated with radical prostatectomy *versus* watchful waiting (WW) (39).

All authors reporting on deferred treatment for presumed localized prostate cancer (Nx-No, Mo) stage T1a, well and moderately differentiated tumors with life expectancy of >10 years, consider that re-evaluation with PSA, TRUS and biopsies of the prostate remnant is necessary.

Furthermore, there is a considerable rate of overdiagnosing tumors which would not be life threatening

if left untreated. Therefore, treatment options such as active surveillance with curative intention of prostate cancer patients with long life expectancy have to be considered. Only in selected patients with favorable tumor characteristics may active surveillance be considered a good and relatively safe alternative option (40).

INDICATIONS FOR RADICAL PROSTATECTOMY

Objectives of radical prostatectomy

Patient selection for radical curative procedures places the urologist in a dilemma of attempting to maintain both the patient quality of life and the length of survival (41). Radical prostatectomy for treatment of prostate cancer can be performed by various techniques using the retropubic, perineal or laparoscopic approach (42-45). Current data would indicate that nerve sparing radical prostatovesiculectomy is the most effective way of dealing with adenocarcinoma of the prostate, which is organ-confined within the anatomic margins of the prostate gland. The experience with radical prostatectomy was more effective than watchful waiting in terms of cancer-specific survival benefit when compared in a prospective randomized trial (31).

Pelvic lymphadenectomy?

The addition of pelvic lymphadenectomy should allow the clinician to assess with greater accuracy the possible presence of extended disease (46). Besides being a staging procedure, extended pelvic lymph node dissection might be curative or at least beneficial in a group of patients with limited lymph node metastases (47). According to Partin nomograms (32), patients with cT1c, PSA value <10 ng/mL and biopsy Gleason score <6 have a low risk of metastatic disease in pelvic lymph nodes, therefore additional advantage of removing lymph nodes may not be necessary.

In patients with intermediate risk (cT2a, PSA value 10-20 ng/mL, biopsy Gleason score 7), or high risk (>cT2b, PSA >20 ng/mL, biopsy Gleason score >8), the presence of pelvic nodal metastases is increased. The addition of extended lymphadenectomy is necessary (46). Joniau *et al.* (49) report an incidence of 13%-27% of overstaging in patients with clinical T3 carcinoma.

Radical prostatectomy as mentioned above is indicated in patients with organ confined prostate cancer, consequently to stages of clinically localized prostate cancer. The goals are complete removal of the gland seminal vesicles and pelvic nodes, while preserving urinary continence and restoring erectile function in good general health in patients with life expectancy of 10 years.

Surgery can be performed with advantages and disadvantages, either as open radical prostatectomy (RRP), laparoscopic approach (LRP) or robotic prostatectomy (RALP) (50). RRP is associated with fewer rectal injuries and pelvic extended lymphadenectomy can easily be performed. LRP achieves a long learning curve with less high costs compared with RALP. Less blood loss, cancer control in lower-intermediate risk patients, preservation of neurovascular bundle can also be achieved using LRP/RALP (51).

Long-term cancer control has been reported in several large series with 10- to 15-year follow up. Freedom from biochemical recurrence was 66% for ORP, 80% for LRP and 72% for RALP in PT2 tumors.

Freedom from progression was 84% for ORP, 97% for LRP and 97.5% for RALP in PT2 tumors. As with other forms of treatment, the probability of recurrence after radical retropubic prostatectomy (ORP) or laparoscopic radical prostatectomy (LRP) or robotic prostatectomy (RALP) varies with the values of clinical and pathologic risk factors. There are no published data on prospective randomized studies (51-53). The average complication rate varies from 2% to 22%/ORP and from 2% to 17% LRP/RALP (54). Loss of urinary control is usually temporary, after 12 months 92% RALP and 79% ORP (55). Erectile function after 12 months achieved acceptable results after bilateral nerve sparing surgery, 93.5%/RALP and 60.6%/ORP (56).

Radical prostatectomy is an effective form of therapy for patients with clinically significant prostate cancer with an acceptable level of morbidity. Although rare, fatal complications do occur.

Experienced surgeons achieve acceptable results with ORP, LRP and RALP. The influence of different surgical techniques reveals similar pathologic and oncologic outcomes comparing RRP, LRP and RALP (57).

Results of treatment of clinical cT3 adenocarcinoma of the prostate with radical prostatectomy are satisfactory. Locally advanced disease can be treated successfully with radical prostatectomy, with a satisfactory overall survival at 5, 10 and 15 years and cancer-specific survival of 95%, 90% and 79%, respectively (48).

POSSIBLE BENEFICIAL EFFECT OF ADJUVANT HORMONAL TREATMENT

Androgen deprivation after radical prostatectomy has been controversially discussed. In the only published prospective randomized study by the Eastern Cooperative Oncology Group (ECOG trial 3886) published by Messing *et al*., patients treated with castration or GnRH therapy after radical prostatectomy with nodal involvement have a significant survival advantage. Hormonal treatment must be administered for two years (59). Detailed investigation by the Early Prostate Cancer Trialists Group shows that the progression free survival is not evident in patients with prostate cancer after standard therapy with additional 150 mg bicalutamide daily. They observed no impact on overall survival in patients with locally advanced prostatic carcinoma (60). Neoadjuvant hormonal therapy (NHT) has been used to facilitate radical prostatectomy and reduce the risk of leaving cancer behind. On the contrary, a review and meta-analysis found a nonsignificant impact on overall and progression free survival (61).

RADIATION THERAPY AND EFFECT OF ADDITIONAL HORMONAL THERAPY

External beam radiotherapy (EBRT), 3-dimensional conformal RT (3D-CRT) and intensity modulated RT (IMRT) improved 10-year PSA relapse free survival (RFS), i.e. 75.6 Gy 85% *versus* 70.2 Gy 58% (62). The European Organization for Research and Treatment of Cancer (EORTC trial 22863) reports the experiences with androgen deprivation therapy (ADT) and EBRT. The investigators demonstrated absolute survival outcomes in patients treated with combined ADT and EBRT compared with those treated with radiotherapy alone (63).

D'Amico *et al*. report that adjuvant hormonal therapy for two years is mandatory in patients undergoing irradiation in the high-risk group (64). The Radiation and Oncology Group (RTOG trial 85-31) report outcomes in patients treated with radiotherapy combined with adjuvant or delayed ADT. They observed better overall survival at 5 years (76% *vs*. 71%) and 10 years (53% *vs*. 38%) in the ADT combined with EBRT group (65). A randomized trial demonstrated improved disease free survival outcomes in patients treated with combined ADT and EBRT compared with conventional radiotherapy alone. Radiotherapy (EBRT) is an effective, noninvasive form of therapy for patients with high-risk (T3-4, Gleason score 8-10 or PSA >20 ng/mL) prostate cancer. Treatment with ADT and 74 Gy for 6 months is standard for intermediate risk patients (T2b-c or Gleason score 7 or PSA 10-20 ng/mL), and for 24-36 months ADT for high-risk patients. ADT combined with EBRT is not advised for patients with low-stage disease (T1a-2a, Gleason score <7, PSA <10 ng/mL) (66).

The Radiation Therapy Oncology Group (RTOG) 92-02 enrolled patients with high-risk prostate cancer. They observed 11% improved overall survival in patients treated for 26 months with ADT compared to 4-month ADT therapy (67). In the RTOG 86-10 study, Roach *et al*. could established that neoadjuvant concomitant and adjuvant hormonal therapy for 6 to 24-36 months in intermediate- and high-risk patients undergoing irradiation improved biochemical disease-free survival (68).

The incidence of erectile dysfunction appears to be related to vascular disruption. Treatment with erectogenic agents can result in response rates ≤70% (69).

BRACHYTHERAPY

The interest in intraprostatic implantation of radioactive material revived in the second half of the 20th century. Transperineal brachytherapy was applied in growths limited to the prostate (category stage cT1b-T2a N0, M0, Gleason score <6) in cases of histologically proven random biopsies. With good International Prostatic Symptom Score (IPSS) with an initial PSA level <10 ng/mL, <50% of biopsy cores involved with prostate cancer on a gland volume of <50 cm^3 is mandatory.

Cancer control after brachytherapy (seeds)

Freedom from biochemical recurrence rate was in the range of 75%-100% at 5 years and 66%-88% at 8-13 years (68). PSA relapse free survival rate for low-, intermediate- and high-risk patients was 82%, 70% and 48% at 7 years (69). Brachytherapy combined with EBRT is needed in the intermediate-risk patient group (70).

Complications and quality of life after low-dose brachytherapy are associated with transient urinary morbidity. Radiation induced urethritis, prostatitis, urgency, dysuria and urinary retention are the most common side effects. They gradually decline during the next 3-6 months (71).

Erectile dysfunction was observed in 30%-40% of patients requiring erectogenic agents that resulted in excellent responses (72).

The use of brachytherapy is an effective noninvasive form of therapy in patients with clinically significant

prostate cancer, with an acceptable level of morbidity. Relative contraindications include previous radiotherapy and inflammatory bowel disease. Brachytherapy is effective for selected patients with clinically confined disease.

Primary treatment options for patients with low- and high-risk factors and localized disease were brachytherapy alone or brachytherapy combined with EBRT.

Biochemical freedom from relapse after modern permanent low-dose rate brachytherapy (LDR-BT) seeds in the low-risk group at 5 years was 70%-95% and at 10 years 65%-89%. However, patients from the intermediate- and high-risk groups experienced no favorable results (73). EBRT is combined with high-dose-rate brachytherapy (HDR-BT) in the intermediate- and high-risk groups. Significant results were achieved with combined treatment (74).

Transient urinary morbidity related to radiation-induced urethritis or prostatitis accounts for the most common side effects. Erectile dysfunction was observed in 30%-40% of patients. These impairments in the quality of life have been shown to gradually improve with time.

RADIOTHERAPY AFTER PT3, PTX R1 – IMMEDIATE OR DELAYED RADIOTHERAPY AFTER RADICAL PROSTATECTOMY

The presence of positive margins after radical prostatectomy correlates with detectable postoperative elevation of PSA (75). Although the presence of elevated PSA following radical prostatectomy denotes residual disease, one has to reconcile the fact that only 7%-10% of patients following radical prostatectomy will develop clinical local recurrence (76,77). Results of this modality approach (immediate postoperative radiotherapy) were presented in a randomized trial (78).

According to data presented by the Organization for Research and Treatment of Cancer (EORTC trial, 22911), clinical or biological 5-year survival was significantly improved (72.2% *vs*. 51.8%) in the immediate adjuvant radiotherapy group (60 Gy) to radiotherapy delayed until local recurrence (70 Gy) in patients after radical retropubic prostatectomy. The radiation effect is limited. It was not seen that this treatment modality improved metastase-free survival and carcinoma specific survival in this group of patients. From these data it is evident that immediate radiation therapy should be the treatment of choice in cases with multifocal positive surgical margins and a Gleason score >7, or in patients with a PSA level ≥0.1 ng/mL one month after radical prostatectomy.

ALTERNATIVE THERAPEUTIC OPTIONS

Radical prostatectomy has remained the reference standard treatment for localized prostate cancer. Surgery of prostate cancer provides histologic evidence of complete tumor removal, including margin status. The lack of histologic proof of complete tumor ablation is an inherited disadvantage of all ablative technologies. However, with cryoablation, the ability to achieve real-time ultrasound imaging of the iceball appears to overcome this challenge. Besides external beam radiation and/or brachytherapy, cryosurgical ablation of the prostate (CSAP) and high-intensity focused ultrasound (HIFU) have recently become available alternative therapeutic modalities in cases with localized prostate cancer (79).

The ideal patients for cryoablation (CSAP) are those with organ-confined prostate cancer. Prostate volume should be <40 mL, PSA serum levels <20 ng/mL and biopsy Gleason score <7. Long-term follow up of 10 and 15 years is the final step needed to definitively determine the role of cryosurgical ablation in the treatment of localized prostate cancer. In general, the treatment population includes patients with life expectancy >10 years, therefore treatment options must be discussed with patients.

Focal therapy is an alternative technique in the treatment of prostate cancer

Considerable technological advances such as improved biopsy and imaging techniques/multiparametric (MRT) magnetic resonance imaging have improved the field of focal ablation. Several techniques (HIFU, cryoablation) have a potential for focal ablation of prostate cancer. Their use should be considered as no standard option. HIFU can be performed as primary whole gland treatment or salvage treatment (lack of long-term oncology outcome, no better than standard therapy) in patients with local recurrence after external radiation therapy (RT) or seeds (BT). Results and side effects have been acceptable but need confirmation in prospective multicenter trials (79).

Cryoablation is a therapeutic option for selected patients with prostate cancer. It is indicated if there are absolute or relative contraindications for radical prostatectomy. In salvage cases for localized prostate cancer, cryoablation is therapy of choice (80). There is a lack of multicenter randomized trials.

MANAGEMENT OF ADVANCED PROSTATE CANCER – PRIMARY HORMONAL THERAPY

Monotherapy

Seidenfeld *et al*. compared monotherapy with antiandrogens *versus* medical (LHRH analogues) or surgical castration or diethylbestrol in patients with locally advanced prostate cancer. The published data show that the 2-year survival (150 mg/daily) *versus* medical or surgical castration in locally advanced prostate was better for castration patients. This study has confirmed that monotherapy is not an alternative to castration (82).

Iversen *et al*. addressed the question of monotherapy with bicalutamide (150 mg/daily) *versus* medical or surgical castration in locally advanced prostatic carcinoma patients with higher PSA levels. There was no significant difference in overall survival. The use of castration potentially contributes to decreased quality of life with more underlying disorders such as osteoporosis and cardiovascular disease (83).

COMPLETE ANDROGEN BLOCKADE (CAB)

The most commonly used treatments are bilateral orchidectomy or medical castration using a luteinizing hormone-releasing hormone (LH-RH) analogue, both of which eliminate the androgens of gonadal origin. These treatments can be used alone or in combination with an antiandrogen, which inhibits the effect of androgens by blocking the androgen receptor (combined androgen blockade, CAB). The review of the available data and cumulative meta-analysis of the leading investigators and clinical groups having studied the value of complete androgen blockade *versus* castration in the treatment of advanced prostate cancer served as a basis for extensive discussion. After 5-year follow up, response results in favor of combination therapy were published by the Prostate Cancer Trialists Collaborative Group (PCTCG) from analysis of 8275 patients. The study suggests improvement in survival and lower mortality with combination treatment (84).

The International Prostate Cancer Study Group (IPCSG) have reported late results (10 years) of a randomized study comparing medical castration *versus* CAB in advanced prostate cancer from analysis of 589 patients. Results of 10-year survival indicated that there was a small, non-significant benefit in favor of CAB flutamide plus LHRH analogue goserelin compared with goserelin alone (85). There is no general recommendation for CAB today, perhaps some patients may benefit from combination therapy (86).

INTERMITTENT ANDROGEN SUPPRESSION (IAS)

No other treatment exists that equals or surpasses androgen ablation in controlling the growth of prostate cancer. Approximately 80% of prostate cancer patients achieve symptomatic and objective responses following androgen suppression, and serum PSA levels decrease in almost all patients. However, for reasons that remain unknown, the cell death process induced by androgen ablation by whatever means fails to eliminate the entire malignant cell population (86) and after a variable period of time averaging 24 months, tumors inevitably recur with increasing serum PSA levels and are characterized by androgen independent growth. Experimental and early clinical experience with intermittent androgen suppression (IAS) suggests that the quality of life is improved and progression to androgen independence may be delayed using reversible androgen suppression and PSA as a trigger point. IAS may offer a 'way out' of the immediate *versus* delayed treatment controversy by balancing the benefits of immediate androgen ablation with reduced treatment-related side effects and expenses.

The effects of intermittent therapy have also been tested in several phase II trials showing the efficacy of IAS in metastatic disease. Available information about IAS is still very limited. For intermittent *versus* continuous therapy, the South West Oncology Group (SWOG trial 9346) randomized 1134 men with stage D2 prostate carcinoma. After 7-month induction with ADT, PSA levels decreased to <4 ng/mL (87). Finally, PSA reduction to <0.2 ng/mL,<4 ng/mL and >4 ng/mL was identified as a significant prognostic factor with regard to survival, achieving 75 months, 44 months and 13 months, respectively, and no significant differences with regard to survival were seen between treatment groups. Hormonal therapy must be administered when PSA levels increase to 10 ng/mL (metastatic disease) and 4 ng/mL in patients with recurrent prostate cancer.

In conclusion, IAS with PSA control three times a month is at present widely offered to patients with prostate carcinoma in various clinical settings. However, many aspects need to be clarified such as timing, duration and type of treatment.

DELAYED OR IMMEDIATE HORMONAL THERAPY (ADT)

In systemic therapy of advanced prostate cancer, a form of hormonal therapy (ADT) is a standard. In patients with symptomatic prostate cancer with positive

nodal disease and/or metastases T3-T4, PSA >25-50 ng/mL, or PSA doubling time <1 year, testosterone lowering therapy is the treatment of choice. In addition, patients with T1b-T2b are candidates for palliative therapy of symptoms. ADT is also indicated as combined or neoadjuvant (radical prostatectomy) therapy. ADT can be used in asymptomatic prostate cancer with metastases.

Furthermore, patients consent is important concerning toxicity, quality of life and prolonging free survival (89).

Moul *et al*. describe their retrospective experience with 1352 patients with biochemical recurrence after radical prostatectomy. In conclusion, immediate hormonal therapy provided benefit in patients with PSA <5 ng/mL only in cases with Gleason score 8-10 or PSA doubling time <12 months (90). Seiler *et al*. have suggested that biochemical recurrence after positive lymph nodes and radical prostatectomy may be possible. After 10-year follow up, overall survival was 75% in patients with one positive lymph node without immediate adjuvant hormonal therapy. The investigators concluded that patients with multiple positive lymph nodes required immediate adjuvant hormonal therapy. In addition, it was shown that immediate hormonal therapy administered at PSA levels >50 ng/mL or PSA doubling time <12 months was associated with increased overall survival (91). Mc Leod *et al*. could not demonstrate the advantage of adjuvant hormonal therapy with bicalutamide in patients with localized disease without radical prostatectomy, in terms of increased overall survival (85). Loblaw *et al*. report on the results of a meta-analysis of 4 randomized studies. Patients treated with immediate hormonal therapy showed decreased mortality without statistical significance (59).

Therefore, the use of delayed or immediate hormonal therapy in patients with no radical prostatectomy is not recommended today. Therapy depends on PSA value, PSA doubling time and Gleason score.

THE SIGNIFICANCE OF RISING PSA AFTER TREATMENT WITH CURATIVE INTENT

While one can take comfort in falling PSA after radical prostatectomy or irradiation of prostate cancer, rising PSA is a cause for considerable concern (92), noting that PSA levels of >0.2 ng/mL after radical prostatectomy were related directly to biochemical recurrence (recurrence of prostate cancer). The new definition of irradiation failure can be specified as a rise of 2 ng/mL above the post-treatment PSA-nadir (lowest value). Roach *et al*. (68) correlated it with recurrence in men with clinically localized prostate cancer. In conclusion, it is possible that distant dissemination may develop following local failure. The existence or re- growth of local residual disease in localized prostatic carcinoma promotes and enhances spread of metastatic disease.

The probability of distant metastases is related to tumor stage, tumor grade and PSA levels pre- and post-treatment. The relapsing patients, however, were those with short PSA doubling time, advanced stage, unfavorable Gleason scale, and rapidly increasing PSA level. Most of these patients would have a metastatic disease. The PSA doubling time (>10-12 months) and slow PSA increase correlate with local recurrence.

On the other hand, these patients may have benefited from more vigorous initial treatment such as possibly with radical prostatectomy, irradiation, or perhaps androgen deprivation as an adjunct to irradiation. Bone scintigraphy and computed tomography may be helpful and sensitive methods to detect a recurrence if serum PSA level is >20 ng/mL, particularly when PSA velocity is >2 ng/mL/year. Additionally, endorectal MRI may be helpful for detecting a recurrence if PSA level is >2 ng/mL.

Finally, new antibody radiolabelled scintigraphy and PET techniques may provide more accurate information for detecting recurrent or metastatic disease of lymph nodes in the future. Thus, more studies are needed to investigate or evaluate these options before they can be recommended for routine use in clinical practice (93).

TREATMENT OF CASTRATION-RESISTANT PROSTATE CANCER (CRPC)

An escape phenomenon occurs after an average of 24-36 months under androgen suppression therapy by surgical castration, LHRH, and steroidal or non-steroidal antiandrogens (94). The majority of patients with metastatic prostate cancer show PSA rising as a sign of androgen-independent but still androgen-sensitive tumor progression.

Castration-resistant prostate cancer (CRPC) is defined by the European Association of Urology (EAU) as follows: testosterone levels (<50 ng/dL or <1.7 nmol/L); three consecutive PSA rising values within 3 weeks, with 2 PSA levels >50% over nadir; antiandrogen withdrawal 4 weeks for flutamide, 6 weeks for bicalutamide; patients show PSA rising despite ADT; metastatic cancer: >2 bone metastases or other location (1).

At the present, our knowledge about treatment of castration-resistant prostate cancer has changed. The antineoplastic approaches include second line hormonal treatment (corticosteroids, inhibitors of the CYP17 enzyme, giving freedom from PSA recurrence for 4-8 months (89).

Ketoconazole, a nonspecific inhibitor of androgen synthesis, showed clinical activity, however, high doses are needed but are associated with significant side effects (neurotoxicity, gastrointestinal intolerance and liver toxicity). In addition, it is recommended to give concomitant hydrocortisone to restore other steroid hormones.

The identification of intracellular androgen synthesis by prostate cancer cells has led to identification of new targets. Several novel strategies such as inhibitor of androgen synthesis (abiraterone) have shown that the disease continues to progress also in the hormone refractory stage. CRPC remains dependent on androgens and signaling through the androgen receptor (95).

A randomized study has shown the usefulness of abiraterone plus prednisone compared to prednisone alone. The benefits have been reported with 4.6 months in significant overall survival, with mild or moderate side effects with secondary mineralocorticoid excess, i.e. fluid retention, hypokalemia and hypertension. It is considered a new standard of care (96,97).

In conclusion, the European Association of Medical Oncology ESMO has recommended the first- and second line hormonal therapy approach for patients with castration-resistant prostate cancer.

CHEMOTHERAPY

In practice, these patients suffer from a castration-resistant symptomatic and metastatic prostate cancer. In the case of localized or disseminated symptomatic metastases, chemotherapy remains the best treatment option (99). Tannock *et al*. report their experience in the first trial (TAX327 study) in patients with metastatic hormone-resistant prostate cancer treated with mitoxantrone and prednisone *versus* docetaxel plus prednisone. They compared docetaxel 75 mg/m^2 3-weekly or 30 mg/m^2 weekly with prednisone 10 mg daily *versus* standard arm of mitoxantrone 12 mg/m^2 3-weekly with prednisone 10 mg daily. The most effective treatment was the 3-weekly regimen, which produced significant 24% improvement in overall patient survival. They demonstrated median survival improvement of 2.4 months in comparison with the control arm (18.9 months *vs*. 17.4 months docetaxel *vs*. 16.5 months mitoxantrone). There also were significant improvements in pain (35% *vs*. 22%), PSA response (45 *vs*. 32%) and quality of life. The toxicity rates were mostly hematologic in most cases (99). Petrylak *et al*. published the second study from the South West Oncology Group trial 99-16; they randomized 770 patients to 3-weekly docetaxel (60 mg/m^2) in combination with estramustine (280 mg daily 1-5) 3-weekly, compared with mitoxantrone and prednisone. A similar result to that seen with TAX327 was observed, with 23% improvement in survival. The median survival improvement was about 2 months (18 months docetaxel *vs*. 16 months mitoxantrone; p=0.008) and 28% reduction in the risk of death (100). These two reported docetaxel based studies must be accepted as the standard of care in patients with CRPC who might be considered for chemotherapy. With a 3-weekly regimen based on docetaxel, there was a statistically significant improvement in the patient quality of life and prolongation of survival by 2 months.

PALLIATIVE THERAPEUTIC OPTIONS – RADIOTHERAPY, CORTISONE, ANALGESICS AND ANTIVOMITING DRUGS

The action of radiotherapy, which is a local treatment, is limited in the case of disseminated lesions and when the origin of pain is difficult to determine. Patients treated by this method are generally in the terminal stage of the disease. Analgesia has been achieved in a large number of cases but it is difficult to evaluate its duration, as these patients often die soon after irradiation, probably because of their already severely impaired status.

Very good results have been published in the literature with bisphosphonates to prevent skeletal complications (101).

We are left with nonspecific analgesia, which has progressed considerably over recent years. The treatment of a patient with advanced disseminated metastases involves simultaneous administration of high doses of morphine and high doses of nonsteroidal, then steroidal anti-inflammatory agents. Zoledronic acid diminished osteoclastic activity in most of the patients. As a result of these advances, pain can be controlled in the majority of patients.

The treatment of patients with symptomatic bone metastases should involve a multimodal and interdisciplinary approach

Bone metastases and skeletal related events (SRE) are frequent complications in terminal stage. Special atten-

tion should be paid to clinical signs of hypercalcemia, chronic pain, and pathologic bone fractures. Treatment approaches currently include oncologic and medical therapy, pain therapy and radiation therapy (102).

In 70%-90% of patients, pain can be relieved by adherence to the WHO cancer pain recommendations (WHO I, non-opioid analgesics; WHO II and WHO III, opioid analgesics) (103). Other treatment options are inhibitors of the Receptor Activator of Nuclear Factor (RANKL) system.

One study showed good outcome comparing time to first SRE, denosumab *vs.* zoledronate 27.7 *vs*.19.4 months (8 month benefit for the former) (104). Additional pain relief with radiotherapy (EBRT), radium 323 or strontium are other alternatives to be considered.

CONCLUSIONS

As an international community, urologists are not only struggling with the dilemma of helping the patient decide on an optimal treatment plan, but they also have to deal with the uniqueness of their patient population, the availability of technology, and the practice bias of their colleagues. In the area of prostate cancer, there are many clinical situations that have more than one treatment option. The essential features of each condition and its management are summarized.

REFERENCES

1. Heidenreich A, Bastian PJ, Bellmunt J *et al*. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 2014; 65:467-79.

2. Cooperberg MR, Lubeck DP, Metha SS, Carroll PR; CaPSURE. Time trends for prostate cancer: implications for outcomes (data from CaPSURE). J Urol 2003; 170: 21-5.

3. Corica FA, Bostwick DG. Clinically unsuspected and undetected (clinical stage TO) prostate cancer diagnosed on random needle biopsy. Urology 1999; 53: 557-62.

4. Klippel KF, Jurincic CD. Prostatakarzinom. In: Krause W, Rothauge C-F, editors. Andrologie: Krankheiten der Prostata. Stuttgart: Ferdinand Enke Verlag; 1991; p. 207-20. (in German)

5. Bray F, Sankila R, Ferlay J, Parkin DM. Estimates of cancer incidence and mortality in Europe in 1995. Eur J Cancer 2002; 38: 99-166.

6. Black RJ, Bray F, Ferlay J, Parkin DM. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. Eur J Cancer 1997;33:1075-107.

7. Farkas A, Marcella S, Rhoads GG. Ethnic and racial differences in prostate cancer incidence and mortality. Ethn Dis 2000;10: 69-75.

8. Galić J. Epidemiologija, čimbenici rizika i rano otkrivanje karcinoma prostate. Med Vjesn 2009;41(1-2): 37-46. (in Croatian)

9. Gronberg H, Damber L, Damber JE. Familial prostate cancer in Sweden: a nationwide register cohort study. Cancer 1996; 77: 138-43.

10. Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC. Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci USA 1992; 89: 3367-71.

11. Sobin LH, Wittekind C, editors.TNM Classification of Malignant Tumours, 6th edn. New York: Wiley-Liss; 2002.

12. Gleason DF. Histologic grading of prostate cancer: a perspective. Human Pathol 1992; 23: 273-9.

13. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol 1974; 111: 58-64.

14. Luboldt H-J, Rübben H. Früherkennung des Prostatakarzinoms. Dtsch Arztbl 2004; 101: A1736-38. (in German)

15. Oliver SE, May MT, Gunnell D. International trends in prostate-cancer mortality in the "PSA-ERA". Int J Cancer 2001; 92(6): 893-8.

16. Andriole GL,Crawford ED, Grubb RL *et al*. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012; 104: 125-32.

17. Schröder FH, Hugosson J, Roobol MJ *et al*. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012; 366: 981-90.

18. Grosman H, Grinspon D, Lopez M, Bellora O, Scorticati C, Mazza O. Free prostate specific antigen index (free PSA)/ total prostate specific antigen (total PSA) accurate cutoff. Rev Arg Urol 2004; 69(4): 235-40.

19. Mihaljević I, Mudri D, Glavaš-Obrovac Lj, Tucak A. Tumorski markeri karcinoma prostate. Med Vjesn 2009; 41(1-2): 21-8. (in Croatian)

20. Romics I. Technique of ultrasound guided prostate biopsy. Med Vjesn 2004; 36(1-4): 43-6.

21. Galić J, Knežević M, Tucak A, Mrčela M. Prikaz i usporedba rezultata dobivenih nakon transperinealne i transrektalne biopsije prostate s uzimanjem 12 bioptičkih uzoraka. Med Vjesn 2004; 36(1-4): 61-7. (in Croatian)

22. Thompson IM, Pauler DK, Goodman PJ *et al*. Prevalence of prostate cancer among men with a prostate-specific antigen level 4.0 ng *per* milliliter. N Engl J Med 2004; 350: 2239-46.

23. Catalona WJ, Smith DS, Wolfert RL *et al*. Evaluation of percentage of free serum prostate-specific antigen to improve specifity of prostate cancer screening. JAMA 1995; 274: 1214-20.

24. Sun L, Moul JW, Hotaling JM *et al*. Prostate-specific antigen (PSA) and PSA velocity for prostate cancer detection in men aged <50 years. BJU Int 2007; 99: 753-7.

25. Veltman J, Goosen T, Laguna P, Wijkstra H, de la Rosette J. New technical improvements for TRUS in the diagnosis of prostate cancer. Eur Urol 2002; Suppl 1: 8-14.

26. Hodge KK, McNeal JE, Terris MK, Stamey TA. Random systematic *versus* directed ultrasound guided transrectal core biopsies of the prostate. J Urol 1989; 142(1): 71-5.

27. Guichard G, Larre S, Gallina A *et al*. Extended 21-sample needle biopsy protocol for diagnosis of prostate cancer in 1000 consecutive patients. Eur Urol 2007; 52: 430-5.

28. Morote J, Lopez M, Encabo G, de Torres I. Value of routine transition zone biopsies in patients undergoing ultrasound-guided sextant biopsies for the first time. Eur Urol 1999; 35: 294-7.

29. Djavan B, Ravery V, Zlotta A *et al*. Prospective evaluation of prostate cancer detected on biopsies 1, 2, 3 and 4: when should we stop? J Urol 2001; 166: 1679-83.

30. Haggman MJ, Macoska JA, Wojno KJ, Oesterling JE. The relationship between prostatic intraepithelial neoplasia and prostate cancer: critical issues. J Urol 1997; 158(1): 12-22.

31. Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI, Pearson JD. Contemporary update of prostate cancer staging nomograms (Partin tables) for the new millennium. Urology 2001; 58(6): 843-8.

32. Chodak GW, Thisted RA, Gerber GS, Johansson JE, Adolfsson J, Jones GW, Chisholm GD, Moskovitz B, Livne PM, Warner J. Results of conservative management of clinically localized prostate cancer. N Engl J Med 1994; 330: 242-8.

33. Albertsen PC, Hanley JA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. JAMA 1998; 280: 975-80.

34. Ochiai A, Troncoso P, Chen M, Lloreta J, Babaian R. The relationship between tumor volume and the number of positive cores in men undergoing multisite extended biopsy: implication for expectant management. J Urol 2005; 174: 2164-8.

35. Zhang L, Loblaw A, Klotz L. Modeling prostate specific antigen kinetics in patients on active surveillance. J Urol 2006; 176: 1392-7.

36. Griffin C, Yu X, Loeb S, Desireddi V, Han M, Graif T, Catalona W. Pathological features after radical prostatectomy in potential candidates for active monitoring. J Urol 2007; 178: 860-3.

37. Klotz L. Active surveillance for prostate cancer: for whom? J Clin Oncol 2005; 23: 8165-9.

38. Wilt TJ, Brawer MK, Jones KM *et al*. Radical prostatectomy *versus* observation for localized prostate cancer. N Engl J Med 2012; 367: 203-13.

39. Bill-Axelson A, Holmberg L, Garmo H *et al*. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med 2014; 370: 932-42.

40. Fröhner M, Wirth M. Organ-und Funktionserhalt beim Prostatakarzinom. Urologe 2014; 53: 1295-301. (in German)

41. Walsh PC. The discovery of the cavernous nerves and development of nerve sparing radical retropubic prostatectomy. J Urol 2007; 177: 1632-5.

42. Grdović C. Usporedba otvorenih i laparoskopskih radikalnih prostatektomija učinjenih na Odjelu za urologiju Opće bolnice Zadar. Med Vjesn 2009; 41(1-2): 79-81. (in Croatian)

43. Vodopija N, Župančić M, Koršić L, Kramer F, Parać I, Krstanoski Z. Laparoskopska radikalna prostatektomija: rezultati kod 140 operiranih bolesnika. Med Vjesn 2004; 36(1-4): 79-84. (in Croatian)

44. Kröpfl D, Zebić N, Roggenbuck U, Burmester L, Mandt D. Radikalna prostatektomija – iskustva stečena liječenjem 801 bolesnika u razdoblju od 1993. do 2003. godine. Med Vjesn 2004; 36(1-49: 69-77. (in Croatian)

45. Winkler C, Bitar A, Klippel K-F. Anterograde retropubic radical prostatectomy (RRP) in 1480 patients. Results of a follow-up study of 300 patients, learning curve and outcome in a retrospective evaluation. Med Vjesn 2004; 36(1-4): 49-53.

46. Heidenreich A, Ohlmann CH, Polyakov G. Anatomical extent of pelvic lymphadenectomy in patients undergoing radical prostatectomy. Eur Urol 2007; 52: 29-37.

47. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999; 281(17): 1591-7.

48. Aus G, Nordenskjold K, Robinson D, Rosell J, Varenhorst E. Prognostic factors and survival in node-positive (N1) prostate cancer – a prospective study based on data from a Swedish population-based cohort. Eur Urol 2003; 43(6): 627-31.

49. Joniau S, Hsu C-Y, Lerut E *et al*. A pretreatment table for the prediction of final histopathology after radical prostatectomy in clinical unilateral T3a prostate cancer. Eur Urol 2007; 51: 388-96.

50. Thüroff JW. Laparoskopische *vs*. Robotische Operationen in der Urologie. Urologe 2012; 51:615-6. (in German)

51. Thomas C, Neisius A, Roos FC, Thüroff JW. Robotisch assistierte radikale Prostatektomie. Urologe 2015; 54: 178-82. (in German)

52. Han M, Partin AW, Pound CR *et al*. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy: the 15 year Johns Hopkins experience. Urol Clin North Am 2001; 28: 555-65.

53. Rassweiler J, Schulze M, Teber D *et al*. Laparoscopic radical prostatectomy with the Heilbronn technique: oncological results in the first 500 patients. J Urol 2005; 173: 761-4.

54. Diaz M, Peabody JO, Kapoor V *et al*. Oncologic outcomes at 10 years following robotic radical prostatectomy. Eur Urol 2015; 67: 1168-76.

55. Saar M, Ohlmann CH, Janssen M *et al*. Die radikale Prostatektomie. Intra-und postoperative Komplikationen erkennen und behandeln.Urologe 2014; 53: 976-83. (in German)

56. Ficarra V, Novara G, Rosen RC *et al*. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. Eur Urol 2012; 62: 405-17.

57. Coelho RF, Rocco B, Patel MB *et al*. Retropubic, laparoscopic and robot-assisted radical prostatectomy: a critical review of outcomes reported by high-volume centers. J Endourol 2010; 24: 2003-15.

58. Busch J, Gonzalgo M, Leva N *et al*. Propensity Score Vergleich der verschiedenen radikalen Operationstechniken beim high risk Prostatakarzinom. Akt Urol 2015; 46: 45-8. (in German)

59. Messing EM, Manola J, Yao J *et al*. Eastern Cooperative Oncology Group study EST 3886: Immediate *versus* deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006; 7: 472-9.

60. McLeod DG, Iversen P, See WA, Morris T, Armstrong J, Wirth MP. Casodex Early Prostate Cancer Trialists Group. Bicalutamide 150 mg plus standard care *vs*. standard care alone for early prostate cancer. BJU Int 2006; 97: 247-54.

61. Bonney WW, Schned AR, Timberlake DS. Neoadjuvant androgen ablation for localized prostatic cancer: pathology methods, surgical end points and meta-analysis of randomized trials. J Urol 1998; 160: 1754-60.

62. Symon Z, Griffith KA, McLaughlin PW *et al*. Dose escalation for localized prostate cancer: substantial benefit observed with 3D conformal therapy. Int J Radiat Oncol Biol Phys 2003; 57: 384-90.

63. Bolla M, Collette L, Blank L *et al*. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomized trial. Lancet 2002; 360: 103-6.

64. D'Amico AV *et al*. Six-month androgen suppression plus radiation therapy *vs*. radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. JAMA 2004; 292(7): 821-7.

65. Pipelich MV, Winter K, Lawton CA, Krisch RE, Wolkow HB, Movsas B *et al*. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys 2005; 61: 1285-90.

66. Bolla M, van Tienhoven G, Warde P *et al*. External irradiation without long-term androgen suppression for prostate cancer with high metastatic risk: 10 year results of an EORTC randomized study. Lancet Oncol 2010; 11: 1066-73.

67. Horwitz EM, Bae K, Hanks GE, Porter A, Grignon DJ, Brereton HD *et al*. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. J Clin Oncol 2008; 26: 2497-504.

68. Roach M, Bae K, Speight J, Wolkow HB, Rubin P, Lee RJ *et al*. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. J Clin Oncol 2008; 26: 585-68.

69. Incrocci L, Hop WC, Slob AK. Efficacy of sildenafil in an open label study as a continuation of a double-blind study in the treatment of erectile dysfunction after radiotherapy for prostate cancer. Urology 2003; 62: 116-20.

70. Zelefsky MJ, Kuban DA, Levy LB *et al*. Long-term multi-institutional analysis of stage T1-T2 prostate cancer treated with permanent brachytherapy. Proceedings of the 47th Annual American Society for Therapeutic Radiology and Oncology Meeting. Int J Radiat Oncol Biol Phys 2005; 63: 33.

71. Davis BJ, Pisansky TM, Wilson TM *et al*. The radial distance of extraprostatic extension of prostate carcinoma: implications for prostate brachytherapy. Cancer 1999; 85: 2630-7.

72. Zelefsky MJ, Yamada Y, Marion C *et al*. Improved conformality and decreased toxicity with intraoperative computer-optimized transperineal ultrasound-guided prostate brachytherapy. Int J Radiat Oncol Biol Phys 2003; 55: 956-63.

73. Merrick GS, Butler WM, Galbreath RW *et al*. Erectile function after permanent prostate brachytherapy. Int J Radiat Oncol Biol Phys 2002; 52: 893-902.

74. Burri RJ, Ho AY, Forsythe K *et al*. Young men have equivalent biochemical outcomes compared with older men after treatment with brachytherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2010; 77: 1315-21.

75. Hoskin PJ, Rojas AM, Bownes PJ *et al*. Randomized trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localized prostate cancer. Radiother Oncol 2012; 103: 217-22.

76. Bedalov G, Bartolin Ž, Zeljko Z, Puškar D, Savić I, Radović N, Persec Z, Jurenec F. Radikalna prostatektomija i pozitivni kirurški rubovi. Med Vjesn 2005; 37(1-4): 95-7. (in Croatian)

77. Bottke D, Wiegel T. Adjuvant radiotherapy after radical prostatectomy: indications, results and outcome. Urol Int 2007; 78: 193-7.

78. Porres D, Pfister D, Brehmer B, Heidenreich A. Organbegrenztes Prostatakarzinom mit positivem Resektionsrand. Urologe 2012; 51: 1246-52. (in German)

79. Bolla M, van Poppel H, Collete L *et al*. Postoperative radiotherapy after radical prostatectomy: a randomized controlled trial (EORTC trial 22911). Lancet 2005; 366: 572-8.

80. Baumunk D, Scostak M. Therapie des lokalisierten Prostatakarzinoms mit hochintensivem fokussiertem Ultraschall. Urologe 2015; 54: 183-90. (in German)

81. Witzsch UKF, Becht E. Kryoablation des Prostatakarzinoms. Urologe 2015; 54: 191-201. (in German)

82. Seidenfeld J, Samson DJ, Hasselblad V *et al*. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. Ann Intern Med 2000; 132: 566-77.

83. Iversen P, Tyrell CJ, Kaisary AV *et al*. Casodex (bicalutamide) 150-mg monotherapy compared with castration in patients with previously untreated nonmetastatic prostate cancer: results from two multicenter randomized trials at a median follow-up of 4 years. Urology 1998; 51: 389-96.

84. Prostate Cancer Trialists Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomized trials. Lancet 2000; 355: 1491-8.

85. Tyrrell CJ, Altwein JE, Klippel F, Jurincic-Winkler C *et al*.: for the International Prostate Cancer Study Group. Comparison of an LH-RH analogue (goeserelin acetate, Zoladex) with combined androgen blockade in advanced prostate cancer: final survival results of an international multicentre randomized trial. Eur Urol 2000; 37: 205-11.

86. Loblaw DA, Virgo KS, Nam R *et al*. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol 2007; 25: 1596-605.

87. Bruchovsky N, Rennie PS, Coldman AJ, Goldenberg SL, To M, Lawson D. Effects of androgen withdrawal on the stem cell composition of the Shionogi carcinoma. Cancer Res 1990; 50: 2275-82.

88. Hussain M, Tangen CM, Higano C *et al*. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer – data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol 2006; 24: 3984-90.

89. Mottet N, Bellmunt J, Bolla M *et al*. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing and castration-resistant prostate cancer. Eur Urol 2011; 59: 572-83.

90. Moul JW, Wu H, Sun L *et al*. Early *versus* delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy. J Urol 2004; 171: 1141-7.

91. Seiler R, Studer UE, Tschan K *et al*. Removal of limited nodal disease in patients undergoing radical prostatectomy: long-term results confirm a chance for cure. J Urol 2014; 191: 1280-5.

92. Cookson MS, Aus G, Burnett AL *et al*. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for localized prostate cancer update panel report and recommendations for a standard in the reporting of surgical outcomes. J Urol 2007; 177: 540-5.

93. Salminen E, Hogg A, Binns D, Frydenberg M, Hicks R. Investigations with FDG-PET scanning in prostate cancer show limited value for clinical practice. Acta Oncol 2002; 41(5): 425-9.

94. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999; 281(17): 1591-7.

95. Merseburger AS, Kuczyk MA, Wolff JM. Pathophysiologie und Androgendeprivationstherapie des kastrationsresistenten Prostatakarzinoms. Urologe 2013; 52: 219-25. (in German)

96. Fizazi K, De Bono J, Haqq M *et al*. Final overall survival(s) analysis of COU-AA-301, a phase 3 study of abiraterone acetate plus prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) pretreated with docetaxel. Eur J Cancer 2011; 47(Suppl):2.

97. Solarić M, Šobat H, Kaučić H *et al*. Sistemska terapija raka prostate. Med Vjesn 2009; 41(1-2): 59-67. (in Croatian)

98. ESMO. Prostate cancer: ESMO Clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2007; 18(Suppl): 36-7.

99. Tannock IF, de Wit R, Berry WR *et al*. TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351: 1502-12.

100. Petrylak DP, Tangen CM, Hussain MH *et al*. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004; 361: 1513-20.

101. Saad F, Gleason DM, Murray R *et al*. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002; 94: 1458-68.

102. Rolfes N, Lümmen G. Behandlung von symptomatischen Knochenmetastasen bei urologischen Tumoren. Urologe 2014; 53: 832-9. (in German)

103. Zimmer A, Greul F, Meißner W. Schmerztherapie in der Urologie. Urologe 2013; 52: 585-97. (in German)

104. Lipton A, Fizazi K, Stopeck A *et al*. Superiority of denosumab to zoledronic acid, for prevention of skeletal-related events: a combined analysis of pivotal randomized phase 3 trials. Eur J Cancer 2012; 48: 3082-92.

SAŽETAK

SMJERNICE ZA DIJAGNOZU, ZDRAVSTVENIM STANJEM UVJETOVANU KVALITETU ŽIVOTA I TERAPIJU KARCINOMA PROSTATE – PROTURJEČJA UROLOŠKE ONKOLOGIJE

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Za rano otkrivanje karcinoma prostate danas se preporuča provesti digitorektalnu palpaciju te pratiti povišenje vrijednosti antigena specifičnog za prostatu (PSA). Transrektalna ultrasonografija (TRUS) zajedno s ultrazvučno vođenim biopsijama mogla bi postati najprihvatljivija tehnika utvrđivanja stadija za rano otkrivene karcinome prostate. Kako bi se postigla ranija dijagnoza potrebno je bolje definirati granične vrijednosti za PSA s jasno iskazanom graničnom vrijednosti za slobodni PSA. Tome bi se moglo pridodati i korištenje nomograma te u suspektnim slučajevima ponovljenih biopsija, TRUS-a, koštanih skeniranja i novih slikovnih tehnika u dijagnostici. Terapija s odgodom u kojoj se koriste metode aktivne opservacije i spremnosti na započinjanje terapije čim se pojave znaci brze progresije bolesti mogla bi stoga biti alternativa aktivnoj terapiji u bolesnika s lokaliziranim karcinomom prostate niskoga rizika, očekivanoga životnog vijeka deset godina ili manje. Prospektivna nasumična istraživanja pokazala su da je radikalna prostatektomija učinkovitija nego praćenje i čekanje u pogledu doprinosa preživljavanju kod bolesnika oboljelih od karcinoma. Neoadjuvantna hormonska terapija nema značajan utjecaj na cjelokupno preživljenje, kao ni na preživljenje bez progresije bolesti. U Europi je fokus postavljen na biokemijski relaps bolesti nakon kurativnoga liječenja (poštedna radikalna prostatektomija i/ili radioterapija kod bolesnika niskoga, umjerenoga i visokog rizika sa 72-78 Gy). Adjuvantna androgena deprivacija je terapija izbora kod metastatskoga oblika bolesti, kod bolesnika koje nije moguće izliječiti. Identifikacija unutarstanične androgene sinteze koju provode stanice karcinoma prostate dovela je do identifikacije novih ciljeva te do nekoliko novih strategija i lijekova treće generacije: inhibitora androgene sinteze, potentnijih antagonista androgenih receptora. Karcinom prostate rezistentan na kastraciju ostaje ovisan o androgenima i signalizaciji putem androgenih receptora. Kemoterapija docetakselom u liječenju refraktornog karcinoma prostate postiže značajnije smanjenje boli, bolji odgovor PSA i bolju kvalitetu života u usporedbi s jednostavnim postupcima liječenja boli i komplikacija. Ovaj rad daje pregled ključnih obilježja pojedinih bolesti te načina njihovog liječenja.

Ključne riječi: **karcinom prostate, liječenje, operacijski postupak, kastracija, hormonska terapija, kemoterapija, radioterapija, kvaliteta života**

ASSESSMENT OF MULTIPLE AREAS ON MAGNETIC RESONANCE MIDSAGITTAL BRAIN IMAGES IN MULTIPLE SCLEROSIS PATIENTS*

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The aim of the study was to compare the first and last magnetic resonance images (MRIs) in patients diagnosed with multiple sclerosis (MS) with MRIs of normal subjects. We wanted to investigate the region initially involved in MS patients. In this retrospective study, midsagittal plane was explored on brain MRIs taken at the time when MS diagnosis was established and the last MRI was obtained following treatment for MS. Comparison was done between healthy subjects and patients diagnosed with MS. The measures included the area of corpus callosum, cerebrum, cerebellum, pons, bulbus, fourth ventricle and pituitary gland. As a result, while there was growth in the fourth ventricle area, there was shrinkage in the other areas in MS patients. In women, the tissues involved at the beginning of the disease were pituitary gland, cerebrum and bulbus, and in men corpus callosum and cerebrum. Atrophy was not time-dependent. Assessment of the correlation between the Expanded Disability Status Scale (EDDS) and atrophy revealed an increase in EDDS (disease progression) to be associated with a decrease in the area of cerebrum and corpus callosum in men, and an increase in the fourth ventricular area in women. In conclusion, we demonstrated that pituitary gland atrophy develops in the early stage of MS, especially in women. Additional studies are needed to investigate the phenomenon of early pituitary and bulbus atrophy in women versus late atrophy of these tissues in men.

Key words: multiple sclerosis, brain, midsagittal areas, assessment

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INTRODUCTION

Multiple sclerosis (MS) is a chronic immune mediated, inflammatory, demyelinating disease of the central nervous system (1). New magnetic resonance imaging (MRI) techniques have shown microstructural damage either at white matter or gray matter, proven to be of histopathologic nature (2). Inflammation in MS has been proven, especially in deep white matter, gray matter and interstitial area, so atrophy occurs globally. Atrophy studies performed in MS have revealed the global cerebral volume, white matter and gray matter to be decreased (3). Cortical atrophy has been shown to be more pronounced than atrophy of the gray matter fraction and white matter fraction, also showing slight correlation with the Expanded Disability Status Scale (EDSS) score (4). It has been observed that the most frequent atrophy type is cortical atrophy and corpus callosum atrophy; also, hippocampal atrophy is much notable than global brain atrophy and continues progressively (5).

Pituitary gland is a secreting organ that is formed by adenohypophysis and neurohypophysis. Not many studies have investigated pituitary gland atrophy in

MS. Corticosteroid therapy is the most frequently used mode of MS treatment, mostly administered for 5-10 days. This treatment causes suppression of the at hypothalamus-pituitary-adrenal (HPA) axis (6). This suppression can be reversed spontaneously, as demonstrated by Lević *et al.* (7). HPA axis suppression has been defined as a consequence of long term glucocorticoid utilization. There is evidence for a time-dependent variability in the HPA stress system with an increased cortisol stress response in the first year after diagnosis, along with a more blunted HPA stress response and a diminished Glasgow Coma Scale (GCS) score in subsequent disease stages (8). Dysregulation of the HPA axis has frequently been reported in MS. So far, HPA axis function in MS has predominantly been studied under pharmacological stimulation, which is associated with a series of methodological caveats. The knowledge of circadian cortisol patterns and cortisol awakening response is still limited (9).

During natural course of MS, HPA axis hyperactivation has been observed (10,11). This hyperactivation suggests that HPA activity exerts a protective effect by limiting the potential immune overload in acute lesional inflammation (12,13). However, this activation has been associated with clinical deterioration (8,14). It has been recommended that the activity of HPA axis can be used as a biomarker for the progression of MS (15).

Also, there are conflicting reports about prolonged glucocorticoid treatment in MS, some of them stating that this treatment suppresses the HPA axis (16).

In our study, MRI examinations were performed in patients diagnosed with MS before and at the end of treatment period. Comparison was made for corpus callosum, pituitary gland, pons, bulbus, fourth ventricle and cerebellum on midsagittal plane images with normal subjects having the same anatomic structure. To the best of our knowledge, there is no study on comparison using midsagittal plane. There are many studies of corpus callosum in MS patients, however, none examined midsagittal plane involving other anatomic structures. It has not yet been clarified whether or not hypophyseal atrophy is present in MS. In addition, correlation of MS patient EDDS grades with the area was performed. Moreover, the presence of atrophy in the newly diagnosed areas and the ratio were compared with controls.

In the present study, the aim was to compare the first and last MRIs of patients diagnosed with MS, and with MRIs of normal individuals. In patients with MS, we wanted to investigate the region involved first. Thus, we compared the findings in the first affected region and early stage findings in MS patients with the patient final EDSS scores.

SUBJECTS AND METHODS

Study design

The study was conducted in accordance with the Helsinki Declaration principles and approved by the local institutional Review Board (Decision no. 2014/12). Cranial MRIs of patients admitted to the neurology department of our tertiary center and diagnosed with relapsing remitting multiple sclerosis (RRMS) according to McDonald criteria were retrospectively included in the study (patient group). All patients were under first-line or second- line drug treatment for MS and differences between treatment types were not evaluated. MRIs of normal healthy subjects (admitted for any reason and having normal MRI findings, matched by age and gender) were reviewed from the radiology archives (control group).

Magnetic resonance imaging

Images were obtained with a 1.5 Tesla, Magnetom Symphony (Siemens, Germany) MRI device. Images were saved in Dicom format. T1 weighted images were used in calculations. All measurements were done by the same observer. Images were viewed by using the Onis (Ver. 2.5 Ultimate) software. Anatomic images were framed by this program. This program calculates the area automatically at the end of drawing.

Outcome parameters

Reachable first and last MRIs were included in the study. Minimum 6 months and maximum 48 months had elapsed between the first and last MRIs. In patient group, the initial and latest obtained MRIs were also compared. Seven areas were chosen for measurements on brain MRI in midsagittal plane. The initial MRIs in patients obtained at the time of MS diagnosis, the last MRIs in patients by that time and MRIs of healthy subjects were analyzed. The EDSS of patients at the time of the last MRI were collected from patient files.

Measurements were performed using the measurement technique employed by Venkatasubramanian *et al.* in schizophrenia patients (17).

The midsagittal section was selected using the following inclusion criteria:

- getting the midline section in which septum pellucidum can be seen;
- distinct outline of the corpus callosum;
- easily identifiable cerebral aqueduct;
- clearly visible cortical gyral crests both anteriorly and posteriorly to the corpus callosum; and
- absence of visible intrusion into the gray and white matter.

The first and the last images of patients were compared between each other, and also with control ones. We also analyzed whether or not the time period correlated with area reduction.

Patient records of EDSS scores at the time of the last MRI were retrospectively reviewed and calculated. EDSS scores range between 0 (normal neurologic findings) and 10 (MS-related death) points. Correlation between EDSS scores and decrease in sizes was investigated. Also, the existence and rate of atrophies at the new diagnosis were compared with controls.

In our study, patients were diagnosed with definitive clinical MS and all patients were under immunomodulatory therapy such as interferon and glatiramer acetate for first-line drug treatment such as phingolimod and natalizumab for second-line drug treatment. Assessment of immunomodulatory effect of different immunomodulatory therapies on brain atrophy was not aimed in this study. The number of patients was not sufficient to form a subgroup for this analysis. If plaque formation limited measurement at the anatomic regions investigated, it excluded the measurement. Patient attack was not considered since this condition does not affect brain atrophy.

All measurements were done by one observer. Images at MS diagnosis compared with second images at the last follow up visit, relation according to the time period elapsed between the two images and atrophy were investigated. The respective structures area was calculated in normal subjects and statistically compared. The cranial areas measured are shown in Figures 1 and 2. The measures included the area of corpus callosum, cerebrum, cerebellum, pons, bulbus, fourth ventricle and pituitary gland (Figs. 1 and 2).

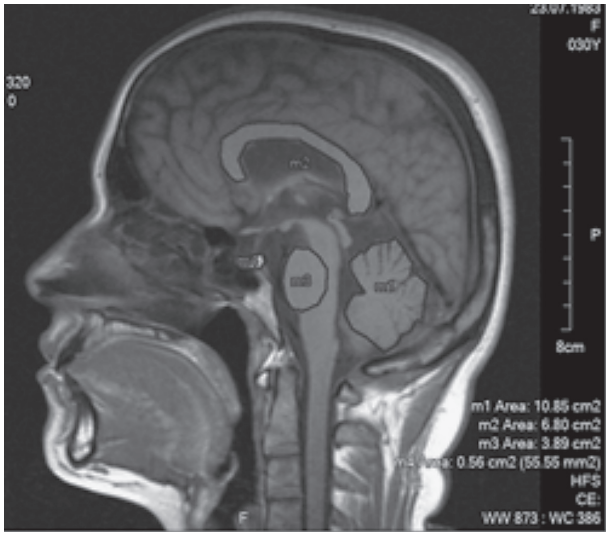

Fig. 1. *Areas: m^1 = cerebellum, m^2 = corpus callosum, m^3 = pons, m4 = pituitary gland*

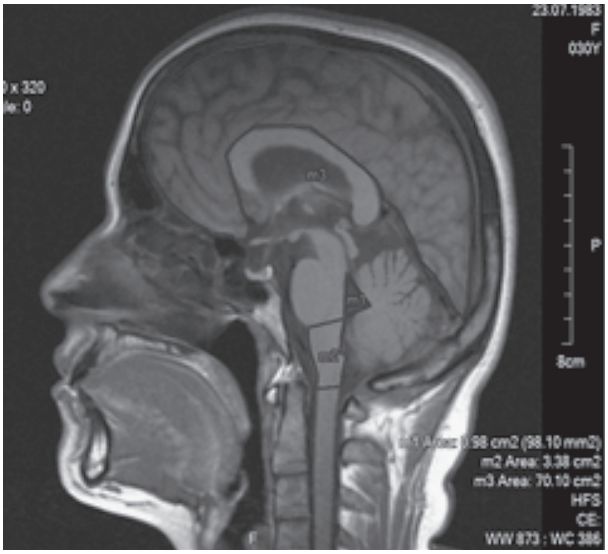

Fig. 2. *Areas: m^1 = fourth ventricle, m^2 = bulbus, m^3 = cerebrum.*

Statistical analysis

Data were analyzed using the IBM Statistical Package for Social Sciences v. 17 (SPSS Inc., Chicago, IL, USA). Parametric tests were applied to data of normal distribution and nonparametric tests were applied to data of non-normal distribution. Student's t-test was used for normal distribution and Man Whitney U test for non-normal distribution. Data were expressed as mean ± standard deviation (SD) or median (interquartile range), as appropriate. All differences associated with a chance probability of 0.05 or less were considered statistically significant.

RESULTS

Brain MRI images in midsaggital plane of 48 patients with RRMS (21 male and 27 female) and 47 healthy control subjects (23 male and 24 female) were analyzed. The mean age of MS patients was 36.33±11.65 and 37.29±11.22 years in female and male patients, respectively. The results obtained were compared with those in 24 female and 23 male healthy subjects, where the mean age was 37.96±9.68 and 40.48±11.93 years, respectively. Data were analyzed according to whether or not fitting normal distribution. The variables showing non-homogeneous distribution in the cerebellum, bulbus, pituitary gland and fourth ventricle were evaluated by Mann-Whitney U test, whereas other variables with homogeneous distribution were expressed as mean ±SD and evaluated by independent sample t-test.

Comparison of initial patient MRIs with control group MRIs revealed the area of bulbus (p=0.04), pituitary

gland (p=0.02), corpus callosum (p=0.0) and cerebrum (p=0.0) to be decreased significantly in the patient group. Comparison of final patient MRIs with control group MRIs showed a significant decrease in the area of corpus callosum (p=0.00), pituitary gland (p=0.00) and cerebrum (p=0.00). These results are shown in Table 1.

Table 1
First and last magnetic resonance imaging (MRI) results in multiple sclerosis and control groups (cm^2) - all subjects

First MRI	Cerebellum	Bulbus	Fourth ventricle	Pituitary gland	Corpus callosum	Pons	Cerebrum
Control group (n=47)	12.03±2.02	4.07±0.48	0.93±0.32	1±0.36	6.35±1.05	3.35±0.43	79.3±7.47
Patient group (n=48)	11.97±2.16	4.2±0.71	0.86±0.24	0.97±0.36	5.39±1.35	3.5±0.37	73.07±7.38
p value	p=0.81	p=0.04	p=0.5	p=0.02	p=0.00	p=0.99	p=0.00
Last MRI	Cerebellum	Bulbus	Fourth ventricle	Pituitary gland	Corpus callosum	Pons	Cerebrum
Control group (n=47)	12.03±2.02	4.07±0.48	1.0±0.36	0.66±0.14	6.35±1.05	3.50±0.43	79.3±7.47
Patient group (n=48)	11.44±2.03	4.07±0.5	1.26±0.75	0.58±0.11	5.00±1.37	3.37±0.4	71.43±7.79
p value	p=0.16	p=1.0	p=0.61	p=0.00	p=0.00	p=0.11	p=0.00

On comparison between the initially obtained MRI images in healthy men and men with MS, a significant decrease was detected in the size of corpus callosum (p=0.00) and cerebrum (p=0.01). Although not statistically significant, the pons, bulbus, cerebellum and pituitary gland were smaller, and the fourth ventricle was larger than their normal sizes. On comparison between the last MRI images in healthy men and men with MS, the areas occupied by corpus callosum (p=0.00), cerebrum (p=0.00) and pituitary gland (p=0.03) were significantly decreased. Although not statistically significant, there was a decrease in the size of the cerebellum and pons, but increase in the area occupied by the fourth ventricle. These results are shown in Table 2.

Table 2
First and last magnetic resonance imaging measurements in multiple sclerosis and control groups – male (cm^2)

Male (first)	Cerebellum	Bulbus	Fourth ventricle	Pituitary gland	Corpus callosum	Pons	Cerebrum
Control group (n=23)	11.85±1.9	4.3±0.49	1.07±0.38	0.63±0.17	6.44±1.18	3.63±0.39	81.63±7.63
Patient group (n=21)	11.75±1.8	4.5±0.52	1.1±0.44	0.57±0.11	5.07±1.25	3.58±0.44	76.07±6.33
p value	p=0.86	p=0.16	p=0.81	p=0.32	p=0.00	p=0.67	p=0.01
Male (last)	Cerebellum	Bulbus	Fourth ventricle	Pituitary gland	Corpus callosum	Pons	Cerebrum
Control group (n=23)	11.85±1.9	4.31±0.49	1.08±0.38	0.63±0.17	6.44±1.18	3.64±0.4	81.63±7.64
Patient group (n=21)	11.25±1.6	4.36±0.52	1.28±0.5	0.54±0.08	4.77±1.4	3.46±0.41	74.55±7.12
p value	p=0.26	p=0.76	p=0.1	p=0.03	p=0.00	p=0.15	p=0.00

When the initially MRI images in healthy women and women with MS were compared, a significant decrease in the areas occupied by the bulbus (p=0.05), cerebrum (0.002) and pituitary gland (p=0.022) was recorded. When the first and last MRI images in healthy women, and in women with MS were compared, a significant decrease was found in the areas occupied by the bulbus (p=0.05), cerebrum (p=0.00) and pituitary gland (p=0.02). Although not statistically significantly, corpus callosum (p=0.06), and fourth ventricle were enlarged, while cerebellum and pons were smaller than normal**.** When the last MRI images of healthy women and women with MS were compared, a significant decrease was recorded in the areas occupied by corpus callosum (p=0.0), cerebrum (p=0.0) and pituitary gland (p=0.02). Despite the lack of any statistical significance, a decrease was found in the size of the cerebellum and pons, and enlargement of the fourth ventricle. Data on MS patient group and control group are shown in Table 3.

Table 3
First and last magnetic resonance imaging measurements in multiple sclerosis and control groups – female (cm^2)

Female (first)	Cerebellum	Bulbus	Fourth ventricle	Pituitary gland	Corpus callosum	Pons	Cerebrum
Control group (n=24)	12.2±2.15	3.85±0.35	0.93±0.32	0.68±0.12	6.27±0.92	3.38±0.42	77.07±6.71
Patient group (n=27)	12.14±2.4	3.97±0.75	0.86±0.24	0.6±0.14	5.63±1.39	3.44±0.31	70.73±7.4
p value	p=0.93	p=0.05	p=0.5	p=0.02	p=0.06	p=0.51	p=0.00
Female (last)	Cerebellum	Bulbus	Fourth ventricle	Pituitary gland	Corpus callosum	Pons	Cerebrum
Control group (n=24)	12.2±2.15	3.85±0.35	0.93±0.32	0.68±0.12	6.27±0.92	3.38±0.42	77.07±6.7
Patient group (n=27)	11.59±2.33	3.85±0.36	1.23±0.9	0.6±0.12	5.19±1.34	3.29±0.38	69±7.53
p value	p=0.33	p=0.95	p=0.27	p=0.02	p=0.00	p=0.46	p=0.00

The following differences were recorded between the first and last MRI images in male MS patients: significant decrease in the areas occupied by the cerebellum (p=0.0), corpus callosum (p=0.0), pons (p=0.05), bulbus (p=0.01), and cerebrum (p=0.00), and enlargement of the fourth ventricle (p=0.00). With the exception of pituitary gland, all measured areas were different between the two groups**.** The following differences were found in the areas occupied by the respective cerebral structures between the first and last MRI images in female MS patients: enlarged fourth ventricle (p=0.04) and significantly decreased areas occupied by the cerebellum (p=0.00), cerebrum (p=0.00), corpus callosum (p=0.00) and pons (p=0.00). No significant changes were recorded in the bulbus and pituitary gland measurements**.** These results are shown in Table 4.

Table 4
Comparison between first and last magnetic resonance imaging (MRI) measurements in male and female MS patients (cm^2)

Male (n=21)	Cerebellum	Bulbus	Fourth ventricle	Pituitary gland	Corpus callosum	Pons	Cerebrum
First MRI	11.75±1.8	4.5±0.52	1.1±0.44	0.57±0.11	5.07±1.25	3.59±0.44	76.07±6.34
Last MRI	11.24±1.6	4.36±0.52	1.28±0.5	0.54±0.08	4.77±1.4	3.46±0.41	74.55±7.12
p value	p=0.00	p=0.01	p=0.00	p=0.61	p=0.00	p=0.05	p=0.00
Female (n=27)	Cerebellum	Bulbus	Fourth ventricle	Pituitary gland	Corpus callosum	Pons	Cerebrum
First MRI	11.59±2.42	3.97±0.75	0.86±0.24	0.6±0.14	5.62±1.39	3.44±0.31	76.73±7.4
Last MRI	11.14±2.33	3.85±0.36	1.24±0.91	0.6±0.12	4.19±1.34	3.29±0.38	69.01±7.54
p value	p=0.00	p=0.33	p=0.04	p=0.55	p=0.00	p=0.00	p=0.00

When the pooled first and last MRIs obtained in MS patients were compared, significant difference was recorded in all the parameters measured except for the bulbus and pituitary gland. These results are shown in Table 5

Table 5
First and last magnetic resonance imaging (MRI) measurements in all MS patient group (cm^2)

Study group (n=48)	Cerebellum	Bulbus	Fourth ventricle	Pituitary gland	Corpus callosum	Pons	Cerebrum
First MRI	11.97±2.16	4.2±0.71	0.96±0.36	0.59±0.13	5.39±1.35	3.5±0.37	73.07±7.39
Last MRI	11.43±2.03	4.07±0.5	1.25±0.75	0.57±0.11	5.01±1.37	3.37±0.4	71.43±7.8
p value	p=0.00	p=0.06	p=0.00	p=0.1	p=0.00	p=0.00	p=0.00

In MS patients, MRI images were obtained at minimum 6 and maximum 48 months apart. There was no significant difference in the time interval between the first and last measurement, or in the atrophy progression in either male or female patients. There was no correlation of the percent differences between the first and last measurements of particular areas in MS patients.

Examination of the correlations between EDSS scores of all male and female MS patients yielded negative (p=0.000) correlation between the first MRI measurements of corpus callosum area and EDSS scores, but positive correlation between EDSS scores and the first measurement of the ventricular area (p=0.001).

In men, there was negative correlation between EDSS scores and the first (p=0.000) and last (p=0.001) measurements of the areas occupied by corpus callosum and cerebrum (p=0.024). In women, the first measurement of the ventricular area correlated positively (p=0.005) with EDSS scores.

As the EDSS scores increased, i.e. as the patient condition worsened, the area of corpus callosum decreased, while that of the fourth ventricle increased.

DISCUSSION

According to recent literature, brain atrophy is present in MS, even in the initial stages of the disease (18). There are many reports stating that brain atrophy occurs due to lesions located both in the gray and white matter (19,20). In our study, we also found that all brain tissues decreased in size, resulting in an increase in the fourth ventricle area. The initial size reduction was observed in the bulbus, pituitary gland, corpus callosum and cerebrum, when we compared first MRIs of MS patients and control subjects. In contrast, there was no significant reduction in the areas of cerebellum and pons on initial scans. The areas of cerebellum and pons were found to be decreased when the last scans were compared with the initial ones. This finding suggested that the cerebellum and pons areas were affected later than the other areas. Atrophy detected in all measured parameters did not correlate with the time elapsed.

In male MS patients, the initial size reduction was observed in corpus callosum and cerebrum, which is consistent with literature data. In female patients, the initial size reduction was observed in pituitary gland and cerebrum.

Hyperactivation of the HPA axis is observed in many patients with MS. This activation is associated with the course of the disease and comorbid mood disorders. Especially in women with secondary progressive disease, correlation was demonstrated between increased cortisol levels and slowly progressing disease. Comparison of patients with higher and lower cortisol levels revealed a relatively greater number of active lesions and smaller number of remyelinated plaques. In patients with MS, hyperactivity of the HPA axis was found to be correlated with lower degrees of inflammation or more severe neurodegeneration. This phenomenon is important in suppression of disease activation (21). MS patients with short illness duration were found to have high cortisol stress response. At long term, however, a significantly decreased HPA activity was recorded. This means that at long term post, the stress glucocorticoid sensitivity decreased. In other words, in the first year, the HPA stress response is high and declines with time. HPA axis activation is regulated by corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). These two types of neurons are located in the paraventricular nucleus of the hypothalamus. HPA activation is provided by neuroendocrine regulation. The recovery in MS was shown to be associated with the activation of the neuroendocrine HPA axis (14).

When evaluated by EDSS, MS patients with gradually higher EDSS scores responded more markedly to cortisol stimulation tests (15). EDSS scores increased more rapidly in patients with stronger HPA reactivity, which was found to be correlated with cognitive affect (16). In another study, indicators of HPA were found to be correlated with neurological disability; however, no correlation between them and duration of the disease, number of previous relapses, corticosteroid therapies or depressive mood was detected (22). In our study, correlation was observed between EDSS scores and decreased areas of cerebrum and corpus callosum in men, and enlargement of the fourth ventricle in women.

All these studies demonstrated that HPA activity, which is increased in the early stage of MS, decreased with time. As a response to preclinical inflammation, hyperactivation of the HPA axis develops. Besides fatigue and mood disorders seen during this stage of the disease, the grade of patient disability worsens. Especially in women, fatigue is most frequently seen during preclinical stage.

In our study, a significant decrease in the areas occupied by the pituitary gland and cerebrum was detected when the first patient MRI images were compared with control group MRIs. When the first and last MRI patient findings were compared and evaluated as a whole or separately for male and female patients, significant differences persisted in all parameters except for the pituitary gland and bulbus, while pituitary gland did not shrink furthermore. This phenomenon demonstrated that pituitary gland was affected in the early stage; however, this effect did not persist at the same level and rate.

The most important and the frequently seen disabling symptom encountered in patients with MS is chronic fatigue (23). Fatigue is seen as the first symptom, along with sensory manifestations in 81% of MS patients du-

ring the first year of the disease (24). In particular, fatigue is found more frequently in women as compared with men (25). The studies performed demonstrated the lack of any correlation between fatigue and MRI findings. Many authors have suggested the presence of probable correlation between basal ganglions and deeply situated structures such as subcortical and frontal circuits, cerebral cortex, thalamus and caudate nucleus, but no satisfactory explanation has been reached (26,27). However, some studies indicated the presence of a relationship between fatigue and HPA axis dysfunction (28,29). In addition, Gottschalk *et al*. performed a study which demonstrated correlation between fatigue felt in MS and hyperactivity of HPA axis (30). Especially in our female patients, atrophy of the pituitary gland was the first manifestation of the disease. Fatigue is seen more frequently in female MS patients and during the first years of the disease. Since our study had a retrospective design, we could not question our patients about their complaints of fatigue. Consequently, we could not evaluate the relationship between atrophy of the pituitary gland and fatigue. Larger scale studies that will investigate the relationship between pituitary atrophy and fatigue in patients with MS are needed.

CONCLUSION

In the literature, numerous studies have reported correlations between MS and MRI findings, especially related to atrophy of the cortex and corpus callosum. However, in our study, differently from other studies, we demonstrated that atrophy of the pituitary gland developed in the early stage of MS, especially in women, but it did not persist at the same level and rate. Therefore, attention should be paid to early atrophy of pituitary gland in women and late atrophy of this tissue in men. Based on our findings, we found that early manifestation of pituitary gland atrophy occurred in female MS patients.

REFERENCES

1. Milo R, Miller A. Revised diagnostic criteria of multiple sclerosis. Autoimmun Rev 2014; 13: 518-24.

2. Ceccarelli A, Bakshi R, Neema M. MRI in multiple sclerosis: a review of the current literature. Curr Opin Neurol 2012; 25: 402-9.

3. Pérez-Miralles F, Sastre-Garriga J, Tintoré M *et al*. Clinical impact of early brain atrophy in clinically isolated syndromes. Mult Scler 2013; 19: 1878-86.

4. Calabrese M, Poretto V, Favaretto A *et al*. Cortical lesion load associated with progression of disability in multiple sclerosis. Brain 2012; 135: 2952-61.

5. Sicotte NL, Kern KC, Giesser BS *et al*. Regional hippocampal atrophy in multiple sclerosis. Brain 2008; 131: 1134-41.

6. Streeten DH, Anderson GH, Jr Dalakos TG *et al*. Normal and abnormal function of the hypothalamic-pituitary-adrenocortical system in man. Endocr Rev 1984; 5: 371-94.

7. Lević Z, Micić D, Nikolić J *et al*. Short-term high dose steroid therapy does not affect the hypothalamic-pituitary-adrenal axis in relapsing multiple sclerosis patients. Clinical assessment by the insulin tolerance test. J Endocrinol Invest 1996; 19: 30-4.

8. Huang TS. Corticotropin secretagogues facilitate recovery of the hypothalamus-pituitary-adrenal axis suppressed by prolonged treatment with dexamethasone. Metabolism 1994; 43: 544-8.

9. Kern S, Rohleder N, Eisenhofer G, Lange J, Ziemssen T. Time matters – acute stress response and glucocorticoid sensitivity in early multiple sclerosis. Brain Behav Immun 2014; 41: 82-9.

10. Kern S, Krause I, Horntrich A, Thomas K, Aderhold J, Ziemssen T. Cortisol awakening response is linked to disease course and progression in multiple sclerosis. PLoS One 2013; 8: e60647.

11. Huitinga I, Erkut ZA, van Beurden D, Swaab DF. The hypothalamo-pituitary-adrenal axis in multiple sclerosis. Ann N Y Acad Sci 2003; 992: 118-28.

12. Ysrraelit MC, Gaitán MI, Lopez AS, Correale J. Impaired hypothalamic-pituitary-adrenal axis activity in patients with multiple sclerosis. Neurology 2008; 71: 1948-54.

13. Schumann EM, Kümpfel T, Then Bergh F, Trenkwalder C, Holsboer FDP. Activity of the hypothalamic-pituitary-adrenal axis in multiple sclerosis: correlations with gadolinium-enhancing lesions and ventricular volume. Ann Neurol 2002; 51: 763-7.

14. Purba JS, Raadsheer FC, Hofman MA *et al*. Increased number of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of patients with multiple sclerosis. Neuroendocrinology 1995; 62: 62-70.

15. Erkut ZA, Hofman MA, Ravid R, Swaab DF. Increased activity of hypothalamic corticotropin-releasing hormone neurons in multiple sclerosis. J Neuroimmunol 1995; 62: 27-33.

16. Gold SM, Raji A, Huitinga I, Wiedemann K, Schulz KH, Heesen C. Hypothalamo-pituitary-adrenal axis activity predicts disease progression in multiple sclerosis. J Neuroimmunol 2005; 165: 86-91.

17. Venkatasubramanian G, Jayakumar PN, Gangadhar BN, Janakiramaiah N, Subbakrishna DK, Keshavan MS. Measuring the corpus callosum in schizophrenia: a technique with neuroanatomical and cytoarchitectural basis. Neurol India 2003; 51: 89-92.

18. Brex PA, Jenkins R, Fox NC *et al*. Detection of ventricular enlargement in patients at the earliest clinical stage of MS. Neurology 2000; 54: 1689-91.

19. Chard DT, Griffin CM, Parker GJ, Kapoor R, Thompson AJ, Miller DH. Brain atrophy in clinically early relapsing-remitting multiple sclerosis. Brain 2002; 125: 327-37.

20. Ge Y, Grossman RI, Udupa JK, Babb JS, Nyul LG, Kolson DL. Brain atrophy in relapsing-remitting multiple sclerosis: fractional volumetric analysis of gray matter and white matter. Radiology 2001; 220: 606-10.

21. Melief J, de Wit SJ, van Eden CG *et al*. HPA axis activity in multiple sclerosis correlates with disease severity, lesion type and gene expression in normal-appearing white matter. Acta Neuropathol 2013; 126: 237-49.

22. Then Bergh F, Kümpfel T, Trenkwalder C, Rupprecht R, Holsboer F. Dysregulation of the hypothalamo-pituitary-adrenal axis is related to the clinical course of MS. Neurology 1999; 53: 772-7.

23. Induruwa I, Constantinescu CS, Gran B. Fatigue in multiple sclerosis – a brief review. J Neurol Sci 2012; 323: 9-15.

24. Kister I, Bacon TE, Chamot E *et al*. Natural history of multiple sclerosis symptoms. Int J MS Care 2013; 15: 146-58.

25. Bensing JM, Hulsman RL, Schreurs KM. Gender differences in fatigue: biopsychosocial factors relating to fatigue in men and women. Med Care 1999; 37: 1078-83.

26. Téllez N, Alonso J, Río J *et al*. The basal ganglia: a substrate for fatigue in multiple sclerosis. Neuroradiology 2008; 50: 17-23.

27. Cantor F. Theme issue central and peripheral fatigue: exemplified by multiple sclerosis and myasthenia gravis. PM&R 2010; 2: 399-405.

28. Maes M, Mihaylova I, De Ruyter, M. Decreased dehydroepiandrosterone sulfate but normal insulin-like growth factor in chronic fatigue syndrome (CFS): relevance for the inflammatory response in CFS. Neuro Endocrinol Lett 2005; 26: 487-92.

29. Cleare AJ. The neuroendocrinology of chronic fatigue syndrome. Endocr Rev 2003; 24: 236-52.

30. Gottschalk M, Kümpfel T, Flachenecker P *et al*. Fatigue and regulation of the hypothalamo-pituitary-adrenal axis in multiple sclerosis. Arch Neurol 2005; 62: 277-80.

S A Ž E T A K

OCJENA MNOGOSTRUKIH PODRUČJA NA SREDNJESAGITALNIM SLIKAMA MAGNETSKE REZONANCIJE MOZGA U BOLESNIKA S MULTIPLOM SKLEROZOM

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Cilj rada bio je usporediti prve i posljednje slike magnetske rezonancije (MR) u bolesnika s multiplom sklerozom (MS) sa slikama zdravih osoba. Kod bolesnika s MS htjeli smo ispitati najranije zahvaćeno područje. U ovoj studiji se srednjesagitalno područje kod bolesnika s postavljenom dijagnozom MS pregledalo na slikama MR mozga u vrijeme postavljanja dijagnoze i nakon liječenja. Uspoređivalo se zdrave osobe s bolesnicima kojima je dijagnosticirana MS. Mjerenje je uključilo područje korpusa kalozuma, mozga, malog mozga, ponsa, bulbusa, četvrtog ventrikula i hipofize. Kod bolesnika s MS došlo je do porasta na području četvrtog ventrikula, a do smanjenja u drugim područjima. Utvrđeno je da su zahvaćena tkiva u žena na početku bolesti bila hipofiza, mozak i bulbus, a kod muškaraca korpus kalozum i mozak. Otkriveno je da atrofija ne ovisi o vremenu. Kada se promatralo korelaciju između zbira na *Expanded Disability Status Scale* (EDDS) i atrofije, vidjelo se da s povećanjem EDDS (kada bolest napreduje) dolazi do smanjenja područja malog mozga i korpusa kalozuma u muškaraca, a povećanja područja četvrtog ventrikula u žena. Pokazali smo da se atrofija hipofize razvija u ranoj fazi MS, osobito u žena. Pozornost privlači rana atrofija hipofize i bulbusa u žena te kasna atrofija ovih tkiva u muškaraca.

Ključne riječi: multipla skleroza, mozak, srednjesagitalna područja, procjena

MASLAČAK *(TARAXACUM OFFICINALE)* KAO MOGUĆI POKAZATELJ RATNIH ONEČIŠĆENJA U ISTOČNOJ HRVATSKOJ

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U širem istraživanju moguće opterećenosti metalima i metaloidima istočne Hrvatske, kao posljedice ratnih zbivanja, proveden je biomonitoring lokalnog stanovništva putem uzoraka seruma, kose i urina te su izuzimani uzorci tla, vode i povrća. S dijelova gdje potpuni povratak i poljoprivredna djelatnost u vidu uzgoja povrća u vrtovima i okućnicama nije u potpunosti uspostavljen, izuzimani su uzorci maslačka, jestivog samoniklog bilja, koje se koristi u prehrani ljudi i životinja. Cilj ovog istraživanja bio je utvrditi da li postoje razlike u koncentracijama metala uspoređujući lokacije visokog inteziteta borbenih djelovanja (LVIBD) sa lokacijama niskog inteziteta borbenih djelovanja (LNIBD). Osim toga pokušala se utvrditi moguća međusobna povezanost kontaminacije metalima u okolišu i kod ljudi, te da li postoji podudarnost po pitanju mogućih „vrućih točaka", mjesta značajno opterećenih metalima. S devet LVIBD izuzeta su ukupno 22 uzorka maslačka, a s 3 LNIBD izuzeto je ukupno 6 uzoraka. Koncentracije metala i metaloida koji se koriste u vojne svrhe (Al, As, B, Ba, Cd, Co, Cr, Cu, Fe, Hg, Li, Mg, Ni, P, Pb, Sb, Si, Sr, U, V i Zn) utvrđivane su postupkom induktivno uspregnute plazme i spektrometrije masa ICP-MS. Povišene koncentracije olova, u odnosu na NDK za tu vrstu namirnica, pronađene su u dva uzorka, kadmija i arsena u jednom uzorku s LVIBD te olova na jednoj LNIBD. Mann Whitney testom testirana je razlika u koncentracijama svakog od 21 elementa između uzoraka prikupljenih na LVIBD i onih prikupljenih na LNIBD. Utvrđena je statistički značajna razlika samo za živu (Hg) (p = 0,035). Koncentracije metala i metaloida u maslačku nisu značajno korelirale s koncentracijama u uzorcima tla. Pearsonovi koeficijenti (biljke/tlo) za svaki pojedini element imali su vrijednosti u rasponu od najniže 0,019 (Ba) do najviše od 0,31 (P). Ipak, analizom glavnih komponenti (PCA) utvrđen je klaster na dvije lokacije na koje značenje ima većina utvrđivanih metala (Mg, Sb, As, B, Sr, U, Cu, Ni, Pb, Si, Ni, Ba, Co, Cr, Li, V, Al, Fe), dok metali Cd i Hg imaju veći utjecaj na preostalim lokacijama. Nešto više koncentracije Sb i Pb „stvorile" su lokaciju Erdutski most intermedijarom između ta dva osnovna klastera, što je sukladno povišenim koncentracijama Al, Fe, Ni i Mg utvrđenim u kosi, tlu i povrću na istoj lokaciji. I maslačak kao indikator onečišćenja okoliša metalima ukazuje da ukupna opterećenost metalima u istočnoj Hrvatskoj nakon Domovinskog rata nije visoka, ali da sukladno analizama tla, povrća i bioloških uzoraka postoje „vruće točke", od kojih je jedna okolica mosta na Dunavu kod Erduta.

Ključne riječi: maslačak, tlo, metali i metaloidi, Domovinski rat, istočna Hrvatska

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UVOD

U Hrvatskoj su ratne aktivnosti trajale od 1991. do 1998. godine, a završile su mirnom reintegracijom istočnih, ranije okupiranih dijelova (1-5). Posljedice ovako dugih ratnih djelovanja na ljudsko zdravlje i okoliš samo su u manjem dijelu istražene (6-9), dok je kontaminacija prisutna i dalje zbog postojanja brojnih minskih polja i opasnost je za stanovništvo i okoliš. Jedna od karakteristika ovog rata bila je prekomjerna

uporaba topništva i zrakoplova što je rezultiralo neselektivnim uništavanjem civilnih ciljeva i infrastrukture, uključujući kuće, bolnice, škole, crkve, mostove, tvornice, itd.. Sve navedeno ostavilo je dugotrajne posljedice (10-12). Neki radovi ukazuju na povišenu učestalost malignih bolesti u poslijeratnom razdoblju, kako u Hrvatskoj, tako i u susjednim zemljama, također zahvaćenih ratom (13-15).

Istraživanje koncentracije metala i metaloida u okolišu u istočnoj Hrvatskoj i mogući učinak na zdravlje stanovništva nije do sada sustavno provedeno. Nedavno su obavljeni prvi rezultati koji se odnose na koncentracije metala i metaloida u uzorcima tla, sakupljenih u istočnoj Hrvatskoj (8). Također su se analizirali raspoloživi vodni resursi ovog dijela Hrvatske (16,17). Obavljena su i uzorkovanja bioloških uzoraka (serum, urin, kosa) kod stanovništva i ratnih veterana s istog područja i ukazala na odstupanja vezana uz izloženost ratnim djelovanjima (7,9,16). Jedno istraživanje utvrdilo je povišenu razinu teških metala u uzorcima bubrega jelena istočne Hrvatske, osobito u starijih životinja, što se možda može povezati s dugotrajnim ratnim djelovanjima (18). Radova koji su istraživali prisutnost metala u povrću ili jestivom samoniklom bilju na području istočne Slavonije praktički nije bilo, uz tek dva rada iz centralnog dijela Hrvatske, koja su istraživala prisutnost teških metala u povrću Zagreba i okolice (19,20).

U usporedbi s uzorcima tla s područja niskih intenziteta borbenih aktivnosti, uzorci tla iz područja intezivnih borbenih djelovanja imali su više koncentracije As, Hg i Pb od dopuštene nacionalnim zakonodavstvom za organski uzgoj, kao i više koncentracije Hg čak i od maksimalno dopuštenih vrijednosti za poljoprivredu općenito (8), s tim da su se kriteriji ponešto promijenili ulaskom Hrvatske u EU. Utvrđena je i „vruća" točka u okolici mosta na Dunavu kod Erduta, gdje su povišene koncentracije Al, Fe, Ni i Mg utvrđene u kosi, tlu i povrću (9).

Maslačak (radič) (*Taraxacum officinale*) je samonikla jestiva biljka i za ovo istraživanje je izabrana jer se koristi u prehrani ljudi i domaćih životinja te kao dio tradicionalne „narodne" medicine (pripravci čaja) (21,22). Osim toga, maslačak raste, kada je riječ o istočnoj Hrvatskoj i na urbanim i ruralnim područjima gdje se poljoprivredna ili privredna djelatnost nije vratila u punom obujmu, kao što su npr. mjesta uz minska polja, neobnovljene kuće i gospodarski objekti i neriješena pitanja vodoopskrbe te općenito infrastrukture, poput škola, vrtića, nedovoljno radnih mjesta i sl. Radi se, dakle, o naseljima gdje se uzgoj povrća na vrtovima i u okućnicama, odnosno povratak u punom smislu riječi nije realizirao.

Glavni cilj i svrha ovog istraživanja bili su utvrditi razine metaloida i metala u uzorcima maslačka sa 28 mjesta uzorkovanja u istočnoj Hrvatskoj. Lokacije uzorkovanja podijeljena su na ona s intenzivnim borbenim djelovanjima (LVIBD) i lokacije niskog intenziteta borbenih djelovanja ili njihovo potpuno odsustvo (LNIBD). Rezultate se je osim po kriteriju izloženosti ratnim zbivanjima željelo usporediti s rezultatima analiza uzoraka tla uzetih na istim mjestima, na isti način i po istim kriterijima, ne bi li se otkrilo postoji li moguća međusobna povezanost kontaminacije metalima u maslačku i tlu, te postoji li podudarnost što se tiče mogućih „vrućih točaka", mjesta značajno opterećenih metalima

MATERIJALI I METODE

Lokacije uzorkovanja

Uzorkovanje je provedeno na 28 mjesta u 12 naselja (dva grada i deset sela), tijekom srpnja 2011. godine (sl. 1). Osam (8) sela i to redom: Vladislavci (tri mjesta uzorkovanja), Dopsin (dva mjesta uzorkovanja), Hrastin (tri mjesta uzorkovanja), Čepin (tri mjesta uzorkovanja), Ćelije (tri mjesta uzorkovanja), Erdut-most (jedan uzorak), Dalj (dva mjesta uzorkovanja), Ernestinovo (tri mjesta uzorkovanja) i grad Osijek (dva mjesta uzorkovanja) bili su lokacije visokog intenziteta borbenih djelovanja (LVIBD) i prikupljena su ukupno 22 uzorka. Dva sela: Potnjani (dva mjesta uzorkovanja) i Draž (dva mjesta uzorkovanja) i grad Našice (dva mjesta uzorkovanja), bile su lokacije niskog intenziteta borbenih djelovanja (LNIBD) i ukupno je sakupljeno 6 uzoraka. Od naselja „pogođenih" ratom, četiri su sela okupirana tijekom rata, spaljena ili zaposjednuta (Ćelije, Erdut, Ernestinovo, Dalj), a četiri sela su bila na prvoj crti obrane (Čepin, Vladislavci, Dopsin, Hrastin), kao i grad Osijek.

Načelo uzorkovanja bilo je kako slijedi: jedan je uzet uzorak s mjesta direktno izloženom djelovanju pješačkog ili topničkog streljiva ili je bilo uz postojeće minsko polje, jedan uzorak uzet je iz centra naselja (obično oko crkve ili škole) i/ili treći uzorak, ako je uzet, bio je izuzet na poljoprivrednom zemljištu, ako je takvo postojalo, na rubu naselja. U kontrolnoj skupini jedan uzorak je uzet iz centra naselja i još jedan s poljoprivrednog zemljišta na rubu mjesta.

Tablica 1.
Prikaz koncentracija metala i metaloida, rezultata Mann Whitneyeva testa te NDK vrijednosti u uzorcima maslačka s područja istočne Hrvatske (μg/kg)(30)

Metali	Lokacije uzorkovanja u odnosu na borbena djelovanja					
	LNIBD* Medijan (SD) N=6	LNIBD* Min Max	LVIBD** Medijan (SD) N=22	LVIBD** Min Max	p	NDK*** μg/kg
Al	316457,2 (580399,7)	10032 1497069	270701,3 (362542,5)	9910 1273618	0,801	-
As	85,2 (141,4)	10,56 **373**	127,7 (347,4)	10 **1678**	0,178	300
B	5040,1 (1771,8)	3380,94 7666	12949,3 (34250,8)	2087 166056	0,484	-
Ba	11345,4 9294,1	1899,73 26232	8212,4 12950,9	1086 62663	0,207	-
Cd	30,1 28,1	0,02 73	76,10 202	0,21 **970**	0,667	200
Co	153,6 191,5	13,6 455	80,6 195,9	11,4 954	0,594	-
Cr	732,1 1151,9	148,73 3074	598,2 1331,6	94,09 6517	0,801	-
Cu	3310,0 2416,9	495,53 7483	6251,4 15771	882 76762	0,977	-
Fe	370875,9 682883,8	57035 1763359	227480,8 364209,3	45112 1744110	0,889	-
Hg	2,8 2,8	0,02 7,3	0,4 0,9	0,02 3	0,035	50
Li	461,2 802,4	34,66 2095	310,0 600,3	45,73 2962	0,844	-
Mg mg/kg	554,7 442,8	138,63 1355	1049,5 2306,5	107,02 11250	0,834	-
Ni	507,9 613,6	104,95 1742	494,3 992,6	74,09 4908	0,888	-
P mg/kg	439,5 193,3	172,42 668	780,1 2003,3	46,87 9702	0,811	-
Pb	173,3 235,5	41,64 **651**	230,1 424,6	51,28 **1980**	0,519	300
Sb	7,0 3,5	3,29 12	11,9 25	0,02 106	0,207	-
Si	69,3 38,5	25,72 113	128,9 326,2	12,94 1583	0,674	-
Sr	3940,5 2475,3	1178 8088	7641,6 17181	1242 84072	0,758	
U	13,3 25,9	0,02 66	8,4 20,1	0,02 97	0,840	
V	569,3 1069	46,48 2744	354,6 790,3	44,82 3861	0,594	
Zn	14351,7 7702	4952 24910	23212,5 63	4223 305480	0,274	

LNIBD*-uzorci s područja NISKOG inteziteta borbenih djelovanja; LVIBD**-uzorci s područja VISOKOG inteziteta borbenih djelovanja; NDK*** - najviše dopuštene količine (30); *p* Mann-Whitney (p=0,05)

Prikupljanje i analiza

Uzorci su sadržavali približno oko 100 grama lišća maslačka, koje je pakirano u spremnike i poslano za daljnju analizu. Listovi su isprani destiliranom vodom, osušeni u pećnici na 80°C tijekom 48 sati, te pulverizirani u fini prah prije analize. Digestija je napravljena pomoću HNO_3 i H_2O_2. Koncentracije elemenata su određene direktnim mjerenjem na ICP-MS i izražene su u mg/kg biljne tvari. Svi su uzorci analizirani korištenjem postupka detekcije elemenata uređajem suspregnute plazme i spektrometrije masa. ICP-MS (ICP-MS, ELAN KRS-e, Perkin Elmer, Waltham, MA, USA). Radni uvjeti ICP-MS su: RF snaga, W 1300, protoka plina plazme 15L/min, sporednog protoka plina 1 L/min, protoka plina raspršivača, 0,93-0,98 L/

min, peristaltičke pumpe brzine 1 mL/min. Instrument je kalibriran nakon svakog 12. uzorka, koristeći vanjski standard s više elemenata u standardnoj otopini (Inorganic Ventures, Christianburg, VA, SAD) i interni standard koji je sadržavao elemente itrij, indij, terbij i bizmut (Anorganic Ventures)(23-26). Princip ICP-MS metode se temelji na induktivno spregnutoj plazmi i spektrometriji masa (engl. ICP-*Inductively Coupled Plasma* i MS-*Mass Spectrometry*), pomoću kojih dolazi do procesa proizvodnje iona i detektiranja i identificiranja iona. Uzorak se uvodi u instrument, prevodi se zatim u aerosol, te zagrijava na 8000˚C u plazmi argona, nakon čega ioni prolaze iz plazme u spektrometar masa i razdvajaju se temeljem odnosa mase naboja; što ih ujedno i identificira (23). Nakon što je uzorak uveden u instrument pomoću automatskog uzorkivača, te je preveden u fini aerosol pomoću raspršivača, pomoću plina argona usmjerava se prema plazmi. Plazma, iako se sastoji od ioniziranih atoma, zadržava elektronski neutralitet. Plazma se pomoću visokofrekventne struje grije na 6 000 - 10 000˚C, te usmjerava kroz tzv. *torch* koji se sastoji od tri koncentrično postavljene kolone (24). Vanjska i unutarnja kolona su kvarcne, dok je središnja napravljena od inertnog aluminijevog oksida. Argon koji formira plinski protok plazme (engl. *plasma gas*) kreće se između vanjske i središnje kolone spiralnim tijekom i najvećom brzinom s osnovnom funkcijom rashlađivanja radi zaštite stijenki kolone. Između središnje i unutarnje kolone teče pomoćni protok argona (engl. *auxiliary gas*) koji sprječava topljenje kolone i nakupljanje soli. Konačno, u centralnoj (unutarnjoj, injekcijskoj) koloni s najmanjim dijametrom, aerosol uzorka se prenosi putem magličastog protoka (engl. *nebulizer gas*) i pomoću visoke temperature raspršuje, isparava te razdvaja na atome i ione (25,27). S obzirom da ICP radi na atmosferski tlak, a MS zahtijeva vakum, to se prevladava sučeljem (engl. *interface*) koji se sastoji od dva cilindra, prvog koji skuplja (engl. *sampler*) i drugog koji obire (engl. *skimmer*) pomoću kojega se uzorak s plinovima pod atmosferskim tlakom prevede u vakuum, uz minimalni utjecaj na sam uzorak. Nakon prolaska kroz interfazni dio, pomoću elektrostatskih leća i ionske optike, ioni se razdvajaju na temelju omjera masa/naboj. Tri su osnovna načina razdvajanja u MS sustavima: kvadripolarni, magnetski i na temelju vremena leta (engl. *time of flight*). Većina ICP-MS uređaja temelji se na kvadripolarnom sustavu. Sastoji se od dva paralelna cilindra u kojima se u električnom polju, nastalom na temelju visokih voltaža, razdvajaju ioni. Pojedine vrste ICP-MS sustava koriste magnetski visokorezolutni analizator, u kojemu se na temelju magnetskog polja skreću ioni različitih masa. U svim ICP-MS instrumentima nakon prolaska kroz maseni spektrometar, ioni udaraju u aktivnu površinu detektora koji elektronskom multiplikacijom proizvodi od kaskade elektrona specifičan puls (26).

Iako se pomoću ICP-MS mogu odrediti vrijednosti svih 66 metala i metaloida za daljnju obradu podataka korišteni su oni koji se koriste u vojne svrhe, a koji su već istraženi na ovom području: Al, As, B, Ba, Cd, Co, Cr, Cu, Fe, Hg, Li, Mg , Ni, P, Pb, Sb, Si, Sr, U, V i Zn.

Statistička analiza

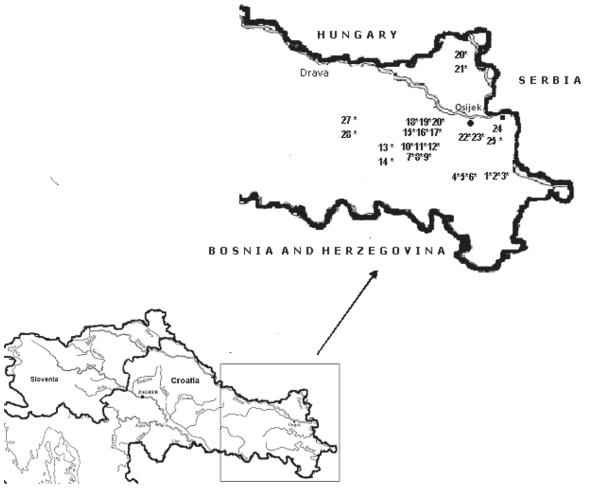
Korištena je deskriptivna statistika (Mann-Whitneyev test i Pearsonov koeficijent) putem programskog paketa Statistica 7.0. Primijenjena je i analiza glavnih komponenti (*Principal Component Analysis* - PCA), kojom se nastojalo istražiti odnose između promatranih varijabli (metala i metaloida) i lokacija uzorkovanja (mjesta)(28,29).

REZULTATI

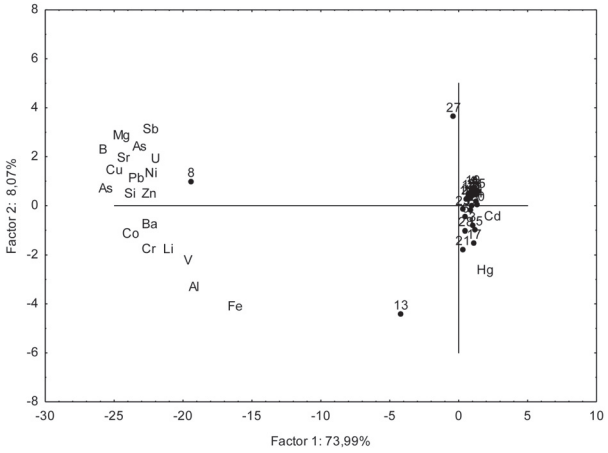
Prosječne vrijednosti koncentracija istraživanih elemenata za oba istraživana područja (lokacije visokog inteziteta borbenih djelovanja (LVIBD) i lokacije niskog inteziteta borbenih djelovanja (LNIBD), minimalne i maksimalne koncentracije, vrijednosti standardnih odstupanja kao i rezultati Mann Whitneyevog U testa te NDK (Najviše Dopuštene Količine) vrijednosti za metale obuhvaćene Pravilnikom za tu vrstu uzoraka (30) prikazani su u tablici 1.

Srednje koncentracije metala obuhvaćenih Pravilnikom o toksinima, metalima, metaloidima te drugim štetnim tvarima koje se mogu nalaziti u hrani (Cd, Pb, As i Hg) bile su ispod NDK (29). Koncentracije kadmija (Cd) i arsena (As) samo su u jednom uzorku s LVIBD (selo Hrastin) premašila NDK za tu vrstu namirnica u hrvatskom zakonodavstvu. Povišene koncentracije olova (Pb) pronađene su u dva uzorka na LVIBD (selo Hrastin i grad Osijek) te u jednom s područja niskog inteziteta borbenih djelovanja (LNIBD) u selu Potnjani.

Mann Whitneyevim testom testirana je razlika u koncentracijama svakog od 21 elementa Između uzoraka maslačka prikupljenih na 22 lokacije izložene borbenim djelovanjima (LVIBD) i onih prikupljenih na 6 „neborbenih" lokacija (LNIBD), statistički značajna razlika nađena je samo u slučaju u slučaju žive (Hg) ($p = 0,035$).



Sl. 1. *Prikaz mjesta uzorkovanja maslačka u istočnoj Slavoniji 2011. godine (Osijek je na 45º32´S i 18º44´I)*



Sl. 2. *Ishodišta (ocjene i opterećenja) u PC1/2 koordinatnom sustavu 28 lokacija uzorkovanja maslačka u Istočnoj Slavoniji i analiziranih 21 metala i metaloida koji se koriste u vojnoj industriji*

Naši rezultati pokazuju da koncentracije metala i metaloida u maslačku nisu značajno korelirale s koncentracijama metala i metaloida u uzorcima tla. Npr. Pearsonovi koeficijenti r (biljke/tlo) za svaki pojedini element imali su vrijednosti u rasponu od najniže 0,19 (Ba) do najviše od 0,31 (P). Čak ni u slučaju Hg nije dokazano prisustvo signifikantnih korelacija između koncentracija žive u maslačku i zemlji na prostoru gdje nije bilo borbenih djelovanja (Pearson r (biljka/tlo)=0,27043 p=0,05) i uzoraka maslačka i zemlje prikupljanih na prostorima s borbenim djelovanjima (Pearson r (biljka/tlo)=0,14 p=0,05).

PCA modelom provedeno je istraživanje na korelacijske matrice u kojoj je 28 mjesta uzorkovanja maslačka (varijabla-mjesta) „opisivalo" 21 element (varijabla-metali i metaloidi). Tumačenje 588 podataka zahtijevalo je vizualizaciju. Sl. 2 prikazuje objekte (28 lokacija) (cca 90 % od ukupne varijacije podataka). Dvije glavne skupine se mogu razlikovati: kompaktna skupina, koja sadrži većinu ispitivanih mjesta u desnom dijelu i dva odvojena klastera (8 i 13) u lijevom dijelu. Očito je većina varijabli (Mg, Sb, As, B, Sr, U, Cu, Ni, Pb, Si, Ni, Ba, Co, Cr, Li, V, Al, Fe) važna uglavnom na mjernim mjestima 8 i 13, a varijable Cd i Hg imaju veći utjecaj na preostalim mjestima. Nešto veće koncentracije Sb i Pb dovele su do toga da se lokacija 27 (Erdutski most) našla kao intermedijer između ta dva osnovna klastera.

RASPRAVA I ZAKLJUČAK

Istraživali smo koncentracije metala i metaloida koji se posredno ili neposredno koriste u ratnim sredstvima (oružju, streljivu, gorivu, uniformama itd…) u maslačku na području istočne Slavonije, u želji da utvrdimo postoji li povezanost s ratnim zbivanjima na tom području u razdoblju od 1991. do 1998. godine. Maslačak je izvrstan fitoindikator. Široko je rasprostranjen, jednostavan za identifikaciju, ima relativno visoku razinu tolerancije na onečišćenje i dobro prikazuje korelaciju između mjerenog onečišćenja (iz tla ili zraka) i koncentracije elemenata u samoj biljci (31). Uzorci su uzimani na područjima gdje se još nije uspostavio uzgoj povrća i to zbog čitavog niza razloga, uz ostalo, prisutnih minskih polja, nepotpune obnove kuća i infrastrukture itd..

Rezultati su pokazali da osim za živu (Hg) ne postoji značajnija razlika između lokacija visokog intenziteta ratnih zbivanja (LVIBD) u odnosu na lokacije niskog inteziteta borbenih djelovanja (LNIBD). Štoviše, Hg je značajnije viša na područjima gdje nije bilo ratnih djelovanja pa se sigurno ne može govoriti o utjecaju rata i tek možemo pretpostaviti što je tome razlog (vjerojatno prirodno veća koncentracija žive na tim područjima).

Utvrđene su povišene vrijednosti olova, kadmija i arsena u po jednom uzorku u selu Hrastin te olova u jednom uzorku uzetom u vojarni u Osijeku. Za Osijek vjerojatno možemo govoriti o utjecaju prisutnosti vojne opreme i sredstava na tom mjestu duže od stoljeća (vojarna još iz vremena Austro-Ugarske) te sigurno o utjecaju prometa budući da se vojarna nalazila u centru grada. Selo Hrastin bilo je na prvoj liniji obrane pa s te osnove sigurno ne čude povišene koncentracije

olova i kadmija, široko korištenih u oružju i streljivu, dok je arsen, uz moguću povezanost s ratnim djelovanjima ipak vjerojatnije povišen zbog svoje prirodne prisutnosti u okolišu u tom području.

Gledajući nadalje druge metale koje ne obuhvaćaju pravilnici u Republici Hrvatskoj, možemo, što implicira da ne predstavljaju veliku ugrozu za zdravlje ljudi, ponoviti da ne postoje razlike između mjesta borbenih djelovanja i onih gdje ih nije bilo ili u puno manjem obimu. Štoviše, poput primjera žive, na područjima niskog inteziteta borbenih djelovanja prosječno su više koncentracije nekih metala (Ni, Cr, Fe, Mg) za koje je poput kroma i nikla poznato da imaju toksični učinak na okoliš. Isto tako, a druga istraživanja su tako pokazala, čak i povišene vrijednosti željeza i magnezija u okolišu mogu imati toksični učinak na testne organizme poput algi i vodenbuhu (32). To također ukazuje na vjerojatno neznatan utjecaj ratnih zbivanja.

Pri interpretaciji ovih podataka treba naglasiti da su izmjerene vrijednosti pojedinih metala niže u odnosu na objavljena istraživanja iz Poljske (industrijski dio Gornje Šleske i ulice Varšave) i ulica kanadskog Montreala (33-35). Uspoređujući ove podatke s istraživanjem Rosselija i sur., koji su istraživali maslačak na različito onečišćenim dijelovima Švicarske, dolazi se do zaključka da su izmjerene vrijednosti kadmija, cinka i bakra ispod razine onoga što su autori nazvali „lagano zagađeni" dijelovi Švicarske (36). Također uspoređujući izmjerene vrijednosti u istočnoj Hrvatskoj sa željezničkim čvorištima u Poljskoj gdje su izmjerene vrijednosti olova, žive, bakra, kadmija, kroma i kobalta također niže, dok su vrijednosti željeza i cinka bile slične (37). Svi ovi rezultati također ukazuju u prilog vjerojatnom antropogenom utjecaju, ali, svakako, mirnodopskog podrijetla.

Ipak, analizom glavnih komponenti (metodom PCA) utvrđen je klaster na dvije lokacije na koji značenje ima većina utvrđivanih metala (Mg, Sb, As, B, Sr, U, Cu, Ni, Pb, Si, Ni, Ba, Co, Cr, Li, V, Al, Fe), dok metali Cd i Hg imaju veći utjecaj na preostalim lokacijama. Nešto više koncentracije olova (Pb), osobito najviše koncentracije stibija (Sb), oslikavaju lokaciju Erdutski most intermedijarom između dvaju osnovnih klastera. To je sukladno utvrđenim povišenim koncentracijama Al, Fe, Ni i Mg u kosi, tlu i povrću na istoj lokaciji, a smatraju se posljedicom intenzivnih ratnih djelovanja po tom mostu i okolici u više navrata i u raznim okolnostima, uključujući bombardiranje od strane NATO-a (8,9,38,39).

Zaključno, i maslačak kao indikator onečišćenja okoliša metalima ukazuje da ukupna opterećenost metalima u istočnoj Hrvatskoj nakon Domovinskog rata nije visoka, ali da sukladno analizama tla, povrća i bioloških uzoraka postoje „vruće točke", od kojih je po svemu sudeći jedna okolica mosta na Dunavu kod Erduta.

L I T E R A T U R A

1. Butković-Soldo S, Brkić K, Puntarić D, Petrovicki Ž. Medical corps support to brigade actions during an attack including river crossing. Mil Med 1995;160: 408-11.

2. Puntarić D, Brkić K. Formation and organization of military medical service at the East Slavonia front in the 1991/92 war in Croatia. Mil Med 1995;160: 412-6.

3. Soldo S, Puntarić D, Petrovicki Ž, Prgomet D. Injuries Caused by Antipersonnel Mines in Croatian Army Soldiers on the East Slavonia Front during the 1991-1992 war in Croatia. Mil Med 1999; 164: 141-4.

4. Puntarić D, Soldo S, Prgomet D, Vodopija R. Type, Severity, Location, and Timing of Battle Casualties in a Croatian Army Brigade During an Offensive Action in 1992. Croatian Med J 1999; 40: 9-13.

5. Puntarić D, Heim I. Morbidity of Croatian Army soldiers in the Osijek Military District in the period July 1, 1991 - September 1, 1993. Croatian Med J 1995; 36: 55-60.

6. Puntarić D, Krajcar D, Bošnir J i sur. Sanitation of the liberated territories in Croatia after the *Storm Campaign* - an example of the Lika-Senj County. Mil Med 1997; 162: 333-7.

7. Jergović M, Miškulin M, Puntarić D, Gmajnić R, Milas J, Sipos L. Cross-sectional Biomonitoring in Adult Populations in Post-war Eastern Croatia: Diffrences Between Areas od Moderate and Heavy Combat. Croat Med J 2010; 51: 451-60.

8. Vidosavljević D, Puntarić D, Gvozdić V i sur. Soil contamination as a possible long term consequence of war in Croatia. Acta Agricult Scand-Soil&Plant Sci 2013; 63: 322-9.

9. Vidosavljević D, Puntarić D, Gvozdić V i sur. Trace metals in the environment and population as possible long term consequence of war in Osijek-Baranja County, Croatia. Coll Antropol 2014; 38: 925-32.

10. Tanner, M. Croatia - A nation forged in war. New Haven/ London: Yale University Press, 1997.

11. Domazet Lošo D. Hrvatski Domovinski rat 1991.-1995.: strateški pogled. Zagreb: Udruga Hrvatski Identitet i Prosperitet-ogranak Matice Hrvatske, 2010.

12. Marcikić M, Marušić A. The civilian massacre in Dalj on 1 August 1991. Lijec Vjesn 1991;113: 202-5.

13. Ebling B, Kovačić L, Ebling Z, Vlahušić A, Tokalić M. Present state and possibilities for improvement of cancer prevention and early detection in the Osijek-Baranya county. Coll Antropol 2005; 29: 169-78.

14. Obralić N, Gavrankapetanović F, Dizdarević Z i sur. The number of malignant neoplasm in Sarajevo region during the period 1998-2002. Med Arh 2004; 58: 275-8.

15. Petrović B, Kocić B, Filipović S, Rančić N., Filipović A. Epidemiology of breast cancer in the city of Niš, Serbia. J BUON 2003; 8: 147-50.

16. Ćurković M. Prisutnost i mogući zdravstveni utjecaj rijetkih elemenata u vodi za piće i biološkim tkivima ruralnog stanovništva istočne Hrvatske. Doktorska disertacija. Osijek: Medicinski fakultet Osijek, 2010.

17. Gvozdić V, Brana J, Orešković K i sur. Analysis and assessment of available water sources in eastern Croatia. Revue Roumaine de Chimie 2015; 60(10): 935-41.

18. Lazarus M, Vicković I, Šoštarić B, Blanuša M. Heavy metal levels in tissues of red deer (*Cervus elaphus*) from Eastern Croatia. Arh Hig Rada Toksikol 2005; 56: 233-40.

19. Bošnir J, Puntarić D. Lead concentration in Brassicas from Zagreb home gardens. Croat Med J 1997; 38: 143-6.

20. Bošnir J, Puntarić D, Škes I i sur. Toxic metals in fresh water fish from the Zagreb area as indicators of environmental pollution. Coll Antropol 2003; 27(Suppl 1): 31-9.

21. Redžić S. Use of wild and semiwild edible plants in nutrition and survival of people in 1430 days siege of Sarajevo during war in Bosnia and Herzegovina. Coll Antropol 2010; 34: 551-70.

22. Gjorgieva D, Kadifkova-Panovska T, Bačeva K, Stafilov T. Content of toxic and essential metals in medicinal herbs growing in polluted and unpolutted areas of Macedonia. Arh Hig Rada Toksikol 2010; 61: 297-303.

23. Brouwers EE, Tibben M, Rosing H, Schellens JH, Beijnen JH. The application of inductively coupled plasma mass spectrometry in clinical pharmacological oncology research. Mass Spectrom Rev 2008; 27: 67-100.

24. Thomas R. A Beginner's Guide to ICP-MS. Part III: The Plasma Source. Spectroscopy 2001; 16: 26-30.

25. Thomas R. A Beginner's Guide to ICP-MS. Part I. Spectroscopy 2001; 16: 38-42.

26. ELAN DRC-e Hardware Guide. Perkin Elmer/MDS Sciex Instruments, 2005.

27. Holmes L. Determination of thorium by ICP-MS and ICP-OES. Radiat Prot Dosimetry 2001; 97: 117-22.

28. Jolliffe, I. Principal Component Analysis. Encyclopedia of Statistics in Behavioral Science. University of Aberdeen, UK, 2005.

29. Abdi H,Williams L. Principal component analysis. WIREs Comp Stat, 2010; 2: 433-59.

30. Republika Hrvatska. Pravilnik o toksinima, metalima, metaloidima te drugim štetnim tvarima koje se mogu nalaziti u hrani. Narodne Novine 2005: 16.

31. Cook SM, Sgardelis S, Panties JD, Lanaras T. Concentrations of Pb, Zn and Cu in Taraxacum spp. In ralation to urban pollution. Bull Environ Contam Toxicol 1995; 53: 2049.

32. Bošnir J, Puntarić D, Cvetković Ž i sur. Effects of Magnesium, Chromium, Iron and Zinc from Food Supplements on Selected Aquatic Organisms. Coll Antropol 2013; 37: 965-71.

33. Krolak E. Accumulation of Zn, Cu, Pb and Cd by Dandelion in environment with various degrees of metal contamination. Pol J Environ Stud 2003; 12: 713-21.

34. Czarnowsa K, Milewska A. The content of heavy metals in an indicator plant (Taraxacum officinale) in Warsaw. Pol J Environ Stud 2000; 9: 125-8.

35. Marr K, Pyles H, Hendershot W. Trace elements in Montreal urban soils and leaves of Taraxacum officinale. Can J Soil Sci 1997; 11: 385-8.

36. Rosseli W, Rossi M, Saso I. Cd, Cu and Zn contents in leaves of Taraxacum officinale. For Snow Landsch Res 2006; 80: 361-6.

37. Wilkomirski B, Sadnik B, Galera H, Wierzbicka B, Malawska M. Railway transportation as a serious source of organica and inorganic pollution. Water Air Soil Pollut 2011; 218: 333-45.

38. Vidosavljević D. Metali i metaloidi u populaciji, vodi i tlu Istočne Hrvatske kao moguća posljedica dugotrajnih ratnih djelovanja. Doktorska disertacija. Osijek: Sveučilište Josipa Jurja Strossmayera u Osijeku, Medicinski fakultet Osijek, 2014.

39. Puntarić D, Vidosavljević D, Gvozdić V, Mayer D, Puntarić E, Puntarić I. Metali i metaloidi u populaciji, bilju, tlu i vodi Istočne Hrvatske kao moguća posljedica ratnih djelovanja. 3. Hrvatski epidemiološki kongres s međunarodnim sudjelovanjem. Knjiga sažetaka, 2015, 28.

SUMMARY

DANDELION (TARAXACUM OFFICINALE) AS A POSSIBLE INDICATOR OF WAR CONTAMINATION IN EASTERN CROATIA

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Biomonitoring of the local population by analysis of serum, hair and urine samples, and collection of soil, water and vegetable samples was performed as part of a broader investigation of metal and metalloid load as a consequence of war events in eastern Croatia. Samples of dandelion (Taraxacum officinale), an edible wild-grown plant used in human and animal nutrition, were collected in the areas where the return of war displaced persons and agricultural activities in vegetable plots and gardens have not yet been fully implemented. The aim of the study was to establish whether there were differences in metal concentrations between the areas of high- and low-intensity war actions (HIWA and LIWA). Another aim was to assess the potential interdependence of metal contamination in the environment and humans, and the potential association with the 'hot spots', i.e. places heavily loaded with metals. Six and 22 dandelion samples were collected at 3 LIWA and 9 HIWA areas, respectively. The concentrations of metals and metalloids used in war actions (Al, As, B, Ba, Cd, Co, Cr, Cu, Fe, Hg, Li, Mg, Ni, P, Pb, Sb, Si, Sr, U, V and Zn) were determined by the method of inductively coupled plasma mass spectrometry. Relative to the minimum allowable concentration, elevated concentrations of lead were recorded in 2 samples, cadmium and arsenic in 1 sample each from HIWA, and of lead in 1 sample from LIWA areas. Differences in the concentrations of 21 elements between the samples collected in HIWA and LIWA areas were determined by Mann Whitney test, yielding a statistically significant difference only for mercury (p=0.035). Metal and metalloid concentrations measured in dandelion samples did not correlate significantly with those in soil specimens; Pearson's coefficients (plant/soil) for each element ranged from 0.019 (Ba) to 0.31 (P). However, the principal component analysis revealed the majority of hard metals predominating at two locations (Mg, Sb, As, B, Sr, U, Cu, Ni, Pb, Si, Ni, Ba, Li, V, Al and Fe), whereas Cd and Hg had greater impact at the remaining locations. Elevated Sb and Pb concentrations rendered the location of Erdut Bridge an intermediary between the two basic clusters, which was consistent with increased Al, Fe, Ni and Mg concentrations determined in human hair, soil and vegetable from the same area. Dandelion as an indicator of environmental contamination with metals showed that total metal load consequential to Homeland War actions in eastern Croatia was not high; however, analysis of soil, vegetable and biological samples pointed to 'hot spots', one of them being the area of Danube Bridge near Erdut.

Key words: dandelion, soil, metal and metalloids, Homeland War, eastern Croatia

CONTINUOUS RENAL REPLACEMENT THERAPY IN ELDERLY PATIENTS WITH ACUTE KIDNEY INJURY

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Acute kidney injury is one of the most intriguing challenges in medicine, as it is followed by high mortality rates despite the progress in understanding and treating the condition. Elderly patients form a particularly sensitive group, due to the complications that come with age and various comorbid conditions. The aim of the study was to analyse the outcome of patients on CRRT, specifically mortality, loss or recovery of kidney functions, along with parameters which could influence outcome and which could be improved during therapy for a better outcome.

The study included all patients that were treated for acute kidney injury at the Clinical Hospital Centre Rijeka in the last 5 years. Total number of patients was 178, of which 64 were female, and 114 were male. Average age was 74,35 ± 5,46 (65-89). All analyzed patients were treated with continuous renal replacement therapy. Patients were divided into three groups in relation to the outcome (group that passed away, group with the loss and group with the recovery of kidney function).

The most common indications for continuous renal replacement therapy were of cardiogenic (n=89, 50,0%) and infectious etiology (n=52, 29,2%). Mortality in patients with acute kidney injury that were treated with continuous renal replacement therapy in our study was 70,79% (n=126), while recovery of renal function occurred in 6,18% (n=11) of the patients. Permanent loss of renal function was more common than recovery, and it occurred in 23,03% (n=41) of the patients. Analysis of parameters revealed that initial creatinine levels, 24-hour diuresis, glomerular filtration, potassium levels and multiple organ failure can be predictors of acute kidney injury outcome in elderly patients.

Key words: continuous renal replacement therapy, acute kidney injury, elderly, mortality

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INTRODUCTION

Acute kidney injury (AKI) is one of the most intriguing challenges in medicine, as it is accompanied by high mortality rates despite the progress in understanding and treating the condition. AKI is defined as a rapid and varied loss of kidney function which results in a wide spectrum of injuries, ranging from mild to severe (1). Resulting kidney dysfunction leads to the accumulation of waste products as well as a volume and electrolyte disbalance which causes systemic damage (2). AKI is usually clinically diagnosed by RIFLE classification, given by ADQI group, and AKIN classification, given by AKIN group (3). Elderly patients form a particularly sensitive group, due to lower renal reserves and complications which come with age and various comorbid conditions such as hypertension, diabetes, atherosclerosis and heart failure (4). Continuous renal replacement therapy (CRRT) is a variety of extracorporeal blood purification technique used to substitute impaired renal function for a prolonged period (5). Despite the advance in CRRT, it is still characterized by high mortality, especially in elderly patients with AKI (6). It bears some risks, including access-related complications, extracorporeal circuit-associated complications, hemodynamic compromise, electrolyte and metabolic complications together with human factors (7). There is no consensus regarding the right time to

initiate CRRT and it remains an important question for the treatment (8). The aim of the study was to analyze the state of patients treated with CRRT, specifically regarding mortality and loss or recovery of kidney functions, along with parameters which could affect the outcome and which could be improved during therapy for better results.

AIM OF THE RESEARCH

Acute kidney injury is associated with excess mortality rates and information for elderly patients are limited. Therefore, the primary goal of this retrospective study was to determine the mortality of the elderly patients with AKI who underwent CRRT. Comorbidities, etiology and parameters were also observed as a potential predictor of mortality.

METHODS

Patient selection

A retrospective study was conducted in Clinical Hospital Center Rijeka on the elderly patients (≥ 65 years) with AKI. 178 patients were admitted to the intensive care unit between January 1st 2010 and December 31st 2015, including 64 female and 114 male patients. The average age was 74,35 ± 5,46 (65 to 89 years). All participants of the study were treated with continuous renal replacement therapy, which include 147 patients with CVVHD, 20 patients with CVVHDF, 8 patients with CVVH and 3 patients with CVVHDF + OXIRIS. The average time on CRRT was 58.95 ± 53.01 (2-259) hours. This retrospective study was approved by Ethics Committee of Clinical Hospital Center Rijeka and it was conducted according to the principles of the Declaration of Helsinki.

Inclusion criteria

According to the Kidney Disease Improving Global Outcomes (KIDIGO) criteria, AKI is defined as any of the following: increase in SCr by ≥ 26.5 μmol/l (≥ 0.3 mg/dl) within 48 hours; or increase in Scr to ≥ 1.5 times baseline in prior 7 days; or urine volume < 0.5 ml/kg/h for 6 hours (9). Patients with chronic kidney disease (CKD) stage 4 and 5, kidney transplantation and patients younger then 65 years were excluded from the study.

Limitations

Limitations in interpreting the results mostly stem from the fact that the three outcome groups of patients and different in number, especially the dialysis outcome group with a small sample size. Furthermore, future studies should objectivize patient state using standard scoring used in intensive medicine (APACHE II, SPAS II, SOFA) to improve the possible analysis.

Data collection

The data was collected from the Integral hospital information system. The following indicators were recorded: general information, such as age, sex, primary disease, complications; vital signs, such as blood pressure, urine output, temperature, oxygenation; laboratory parameter such as kidney function, blood routine, electrolytes. Patients were divided into three groups and then compared according to the outcome and their baseline characteristics. Groups were non-survival group (n=126), renal recovery group (n=42) and dialysis group (n=11). Mortality was calculated according to the statistical survival time of patients 4 weeks after CRRT, with renal recovery being based on creatinine clearance (30 ml per hour urine flow increase or spontaneous serum creatinine fall).

Statistical analysis

Statistical analysis was performed using descriptive statistics, expressed as the mean ± standard deviation of minimal and maximum value. One-way ANOVA was used for normally distributed samples, which were additionally verified using the Kruskal-Wallis test due to the low sample count in one of the groups. Kruskal-Wallis test was also used for comparing the non-parametric samples of independent groups. P value of <0.05 has been considered statistically significant. Statistical analysis was performed using the MedCalc 10 software (MedCalc, Mariakerke, Belgium).

RESULTS

Total number of analyzed patients was 178, consisting of 114 male (64.04%) and 64 female (35.96%) patients, mean age 74.35 ± 5.46 (65-89), who were treated with continuous renal replacement therapy due to AKI. The most common indication for CRRT was of cardiac (n=89) and infective etiology (n= 52). The mean time of CRRT in patients was 58.95 ± 53.01 hours. The mortality rate was 70.79% (126 patients), 23.03% (41 patients) recovered renal function with no need for further renal replacement therapy, while 6.18% (11 patients) required renal replacement therapy. There were no statistical significant differences among groups in the gender (p=0.677) and the mean age (p=0.634)(Table 1).

Table 1.
Characteristics of patients treated with CRRT.

Demographics	Total patients	178
	Age (y)	74.35 ± 5.46 (65-89)
	Sex (M/F)	114 (64.04%) / 64 (35.96%)
Causes of AKI/ CRRT indication (%)	Ischemia	76 (42.70%)
	Sepsis/Infection	62 (34.83%)
	Surgery	40 (22.47%)
Comorbidities (%)	Diabetes	59 (33.15%)
	Hypertension	124 (69.66%)
	Cardiopathies	145 (81.46%)
Outcome (%)	Death (non-survival)	126 (70.79%)
	Dialysis	11 (6.18%)
	Renal function recovery	41 (23.03%)

Initial levels of serum creatinine were statistically higher in the dialysis outcome group (649.81 ± 332.89) compared to the renal recovery group (341.05 ± 164.05) and non-survival group (420.07 ± 200.78), which had no mutually significant difference (Figure 1A). Creatinine levels at the end of CRRT were highest in the dialysis group (407.00 ± 227.92) and non-survival group (294.06 ± 158.82), which were both statistically higher than the renal recovery group (185.82 ± 108.6). However, there was no statistically significant differences between the two former groups in end creatinine levels (Figure 1B). Furthermore, measured 24-hour diuresis was only significantly higher in the renal recovery group (782.33 ± 675.05) compared to the non-survival group (541.76 ± 863.73) (Figure 1C). Interestingly, initial glomerular filtration rates were rather different between all three groups. The renal recovery group had significantly higher GFR (19.25 ± 9.94) compared to both groups, while the dialysis group had the lowest GFR of the three groups (8.00 ± 5.47) (Figure 1D). Measuring initial potassium revealed a mild, statistically significant, hyperkalemia in the non-survival group (5.30 ± 1.06) compared to the renal recovery group (4.77 ± 0.83). The renal recovery and the dialysis groups (5.01 ± 0.84) had normal potassium levels, although the latter had borderline levels (Figure 1E). Finally, the analysis of multiple organ dysfunction revealed a greatly increased incidence in the non-survival group (n=57. 45%) compared to the renal recovery group (n=9. 23%) and the dialysis group (n=2. 18%) (Figure 1F).

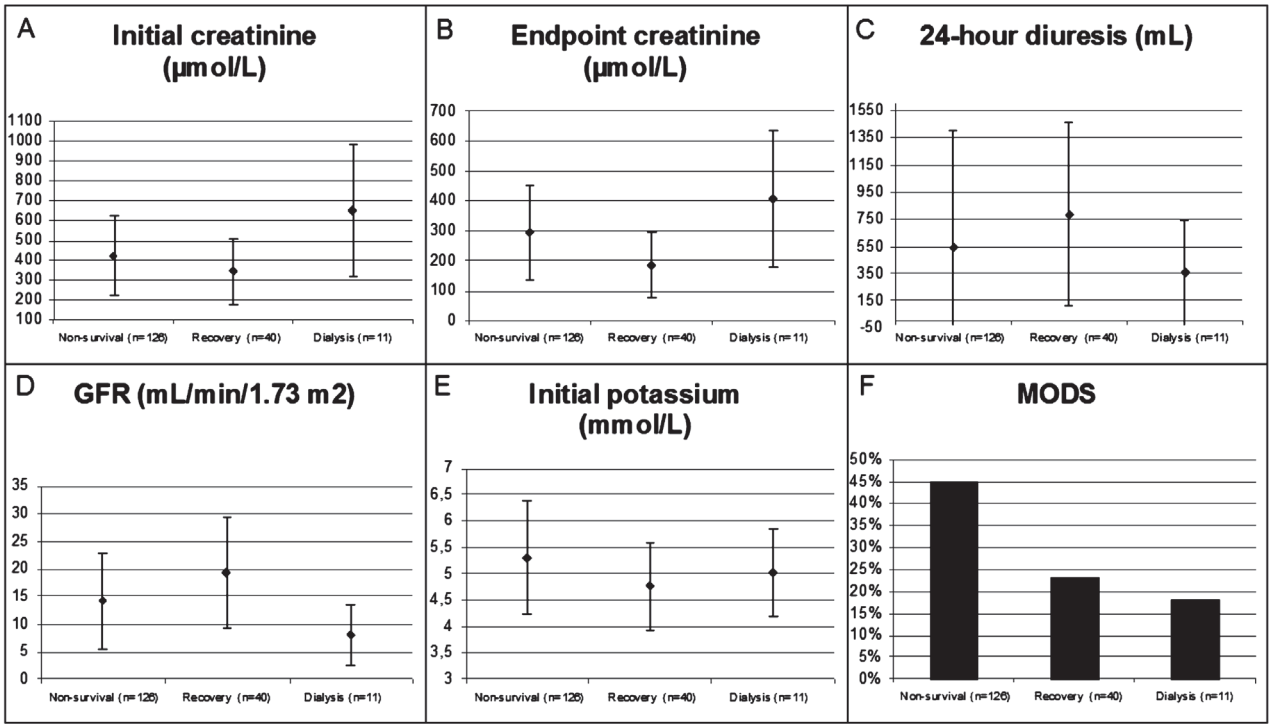

Fig. 1. *Results of the kidney function, postassium and MODS.*
Initial levels of serum creatinine were statistically higher in the dialysis outcome group (649.81 ± 332.89) compared to the renal recovery group (341.05 ± 164.05) and non-survival group (420.07 ± 200.78), which had no mutually significant difference (Figure 1A). Creatinine levels at the end of CRRT were highest in the dialysis group (407.00 ± 227.92) and non-survival group (294.06 ± 158.82), which were both statistically higher than the renal recovery group (185.82 ± 108.6). However, there was no statistically significant differences between the two former groups in end creatinine levels (Figure 1B). Furthermore, measured 24-hour diuresis was only significantly higher in the renal recovery group (782.33 ± 675.05) compared to the non-survival group (541.76 ± 863.73) (Figure 1C). Interestingly, initial glomerular filtration rates were rather different between all three groups. The renal recovery group had significantly higher GFR (19.25 ± 9.94) compared to both groups, while the dialysis group had the lowest GFR of the three groups (8.00 ± 5.47) (Figure 1D). Measuring initial potassium revealed a mild, statistically significant, hyperkalemia in the non-survival group (5.30 ± 1.06) compared to the renal recovery group (4.77 ± 0.83). The renal recovery and the dialysis groups (5.01 ± 0.84) had normal potassium levels, although the latter had borderline levels (Figure 1E). Finally, the analysis of multiple organ dysfunction revealed a greatly increased incidence in the non-survival group (n=57. 45%) compared to the renal recovery group (n=9. 23%) and the dialysis group (n=2. 18%) (Figure 1F).

DISCUSSION

In 1977 the continuous arteriovenous hemofiltration, which was the predecessor od today's CVVHDF, was described by Kramer for the first time. (10). Although further improvement of the continuous replacement therapy contributed to greater survival rates, mortality is still high. Particularly sensitive and vulnerable group are elderly patients (≥65 years). Due to their physiological aging, anatomic and structural changes in the kidney lead to the functional deterioration, which presents itself as a decrease in glomerular filtration rate and renal blood flow (11). Age-related changes occur in every organ system and they vary from one individual to another (12). A mixture of aging, complications and various comorbidities lead to a condition susceptible for diseases.

Acute kidney injury is related to the high mortality rate, which amount from 40% to 70% in general population (13). Metnitz *et al.* performed a prospective, multicenter study in Austria to explore the association between AKI and the mortality rate. The prevalence of patients with AKI, who underwent CRRT, was 4,9% in the intensive care unit. Their mortality rate was 62.8% with mean age 65.2 ± 15.2 years (14). Uchino *et al.* conducted a prospective, multicenter and multinational study about AKI in critically ill patients in intensive care unit. The mean age of observed patients was 67 years (53-75 years) and the overall mortality rate was 60,3%.One of the goals was to determine the prevalence of AKI requiring RRT and it was from 5% to 6% (15). Liu *et al.* have reported 60,98% mortality rate for elderly patients, mean age 88,65 ± 4,76 years (16), while Gong *et al.* have reported 42% mortality rate with mean age 77.89 ± 7.86 years (4). In this study, despite the younger average age (74.35 ± 5.46 years), the analyzed patients had a higher mortality rate (70.79%). The Eurostat statistical information shows that the European population is aging and the life expectancy is increasing. The percentage of elderly people in 2015 in France was 18,4%, in Austria and Spain 18.5%, in Croatia 18.8, in Germany 21.0% and in Italy 21.7% (17). Therefore, studying diseases and differences in connection with age is needed and relevant.

Furthermore, no difference was found in gender and age among analyzed groups, which is in accordance with the studies performed by Gong *et al.* and Liu *et al.* (4)(16). As in this study, Yokota *et al.* also did not find any correlation between concomitant diseases, like hypertension, diabetes mellitus, and cardiovascular diseases, and an excess risk of death (18). Interestingly, Gong *et al.* reveal that concomitant diseases present in elderly patients with AKI are an independent risk factor for death and the most frequent ones are cardiovascular diseases, diabetes, sepsis and hypertension. The main causes of AKI in this study with elderly patients, who underwent CRRT, were ischemia (n=76, 42.70%), sepsis/infection (n=62, 34.83%) and surgery (n=40, 22.47%), while Gong *et al.* had a smaller number of sepsis (n=10, 10.10%), but more ischemic causes (n=53. 54%), then surgery (n=33, 33.33%) and nephrotoxic drug (n=3, 3.03%)(4).

Creatinine levels measured initially and creatinine levels measured at the end of CRRT were the highest in the dialysis group, compared to the other groups, which had no mutually significant differences. High serum creatinine in the dialysis group was elucidated with etiology of AKI, which is chronic kidney disease, stage 1 to 3 (stages 4 and 5 were excluded). However, the difference among the non-survival and the renal recovery group is consistent with results from Liu *et al,* who completely excluded patients with chronic kidney disease (stage 1 to 5) (16). Furthermore, a significantly higher urine output measured over a 24-hour period was present only in the renal recovery group, compared to the non-survival group, which tells us that 24-hour diuresis can be one of the predictors of outcome in AKI. Beside diuresis, glomerular filtration rate provides information about kidney function. Initial glomerular filtration rates were significantly different between analyzed groups. The renal recovery group had the highest GFR among all three groups, while the dialysis group had the lowest GFR, due to the chronic kidney disease (stage 1 to 3) in the background. Therefore, initial GFR can be one of the predictors of outcome. Interestingly, statistically significant difference in initial potassium was noticed between non-survival and renal recovery group, but not between non-survival and dialysis group. However, Gong *et al.* have reported normal potassium levels in the non-survival group (4.0 mmol/L, 3.7-4.9), as well as in the survival group (4.2 mmol/L, 3.7-4.7) (4), which is more preferable, because inadequate potassium regulation can precipitate or result in life-threatening condition (19). According Gong et al., MODS was independent risk factor in the death of patients with AKI. The mean mortality rate for elderly patients was 42% and it was increasing with the number of failed organs. With the dysfunction of 2 organs, the mortality rate was 39%, 3 organs was 50%, 4 organs was 60% and 100% for the dysfunction of 5 organs (4). In this study the non-survival group had higher incidence of MODS (45%) compared to the renal recovery group (23%) and the dialysis group (18%). Therefore, MODS is one of the predictors of mortality. Liu *et al.* also reported that MODS increased incidence of mortality (16). Yokota *et al.* found that elderly patients with septic complications are prone to develop MODS, which increases the risk of mortality (18).The results summary between the three analyzed groups were shown in Table 2.

Table 2.
Results summary between the three groups.

	NON-SURVIVAL (N=126)	RENAL RECOVERY (N=41)	DIALYSIS (N=11)	P
Age (y)	74,45 ± 5,54	74,29 ± 5,42	72,81 ± 4,91	0,634
Sex (% M)	82 (65)	24 (58)	6 (54)	0,677
24-hour diuresis (mL)	541,76 ± 863,73	782,33 ± 675,05	357,00 ± 389,35	<0,05
Initial creatinine (μmol/L)	420,07 ± 200,78	341,05 ± 164,05	649,81 ± 332,89	<0,05
Endpoint creatinine (μmol/L)	294,06 ± 158,82	185,82 ± 108,6	407,00 ± 227,92	<0,05
Initial potassium(mmol/L)	5,30 ± 1,06	4,77 ± 0,83	5,01 ± 0,84	<0,05
Initial urea (mmol/L)	26,05 ± 12,63	22,39 ± 11,48	26,34 ± 12,76	0,262
GFR (ml/min/1.73 m2)	14,21 ± 8,65	19,25 ± 9,94	8,00 ± 5,47	<0,05
MODS [(n)%]	57 (45)	9 (23)	2 (18)	<0,05
Surgical procedure [(n)%]	67 (53)	25 (61)	4 (45)	0,565

Abbreviations: CRRT – continuous renal replacement therapy; GFR – glomerular filtration rate; MODS – multiple organ dysfunction syndrom;

CONCLUSIONS

This study found out that the mortality rate of elderly patients with AKI, who underwent CRRT, was 70,79%, and that 24-hour diuresis, GFR and MODS were independent risk factors for the death.

REFERENCES

1. Case J, Khan S, Khalid R, Khan A. Epidemiology of acute kidney injury in the intensive care unit. Crit Care Res Pract. 2013; 2013: 479730.

2. Abdel-Kader K, Palevsky PM. Acute kidney injury in the elderly. Clin Geriatr Med 2009; 25: 331-58.

3. Lopes JA, Jorge S. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. Clin Kidney J 2013; 6: 8-14.

4. Gong Y, Zhang F, Ding F, Gu Y. Elderly patients with acute kidney injury (AKI): clinical features and risk factors for mortality. Arch Gerontol Geriatr 2012; 54: e47-e51.

5. Pannu N, Gibney RN. Renal replacement therapy in the intensive care unit. The Clin Risk Manag 2005; 1: 141-50.

6. Coca SG. Acute kidney injury in elderly persons. Am J Kidney Dis 2010; 56: 122-31.

7. Palevsky PM, Baldwin I, Davenport A, Goldstein S, Paganini E. Renal replacement therapy and the kidney: minimizing the impact of renal replacement therapy on recovery of acute renal failure. Curr Opin Crit Care 2005; 11: 548-54.

8. Kellum JA, Mehta RL, Angus DC, Palevsky P, Ronco C. The first international consensus conference on continuous renal replacement therapy. Kidney Int 2002; 62(5):1855-63.

9. Kellum JA, Lameire N, Uhlig K *et al*. Diagnosis, evaluation and management of acute kidney injury: a KIDIGO summary (Part 1). Crit Care 2013; 17: 204.

10. Kramer P, Wigger W, Rieger J, Matthaei DSF. Arteriovenous hemofiltration: a new and simple method for treatment of overhydrated peatients resistant to diuretics. Klin Wochenschr 1977; 55: 1121-25.

11. Weinstein JR, Anderson S. The Aging Kidney: Physiological Changes. Adv. Chronic Kidney Dis 2010; 17: 302-7.

12. Boss GR, Seegmiller JE. Age-related physiological changes and their clinical significance. West J Med 1981; 135: 434-40.

13. Bae WK, Lim DH, Jeong JM *et al*. Continuous renal replacement therapy for treatment of acute kidney injury. Korean J Intern Med 2008; 23: 58-63.

14. Metnitz PGH, Krenn CG, Steltzer H *et al*. Effect of aute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med 2002; 30: 2051-58.

15. Uchino S, Kellum JA, Bellomo R *et al*. Acute Renal Failure in Critically ill Patients; A Multinational, Multicenter Study. JAMA 2005; 294: 813.

16. Liu S, Cheng Q-L, Zhang X-Y *et al*. Application of continuous renal replacement therapy for acute kidney injury in elderly patients. Int J Clin Exp Med. 2015; 8: 9973-8.

17. Eurostat. Population age structure by major age groups, 2005 and 2015. http://ec.europa.eu/eurostat/statistics-explained/index.php/Population_structure_and_ageing.

18. Yokota LG, Sampaio BM, Rocha E, Balibi AL, Ponce D. Acute kidney injury in elderly intensive care patients from a developing country: clinical features and outcome. Int J Nephrol Renovasc Dis 2017; 10: 27-33.

19. Lenhardt A, Kamper MJ. Pathogenesis, diagnosis and management of hyperkalemia. Pediatr Nephrol 2011; 263 77-84.

SAŽETAK

KONTINUIRANO NADOMJEŠTANJE BUBREGA KOD STARIJIH BOLESNIKA S AKUTNOM OZLJEDOM BUBREGA

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Akutna bubrežna ozljeda je jedan od intrigantnijih problema medicine, budući da je i dalje prati visok mortalitet unatoč napretku u liječenju i razumijevanju same bolest. Posebno osjetljivu skupinu čine stariji pacijenti, koji su zbog same dobi i svih komorbiditeta posebno ugroženi. Cilj studije bio je analizirati ishod pacijenata na CRRT-u, odnosno mortalitet, gubitak i oporavak bubrežne funkcije, kao i parametre koji bi potencijalno mogli upućivati na mogući ishod, no na koje bi se ujedno moglo i utjecati u svrhu boljeg preživljenja.

U ispitivanju su sudjelovali pacijenti oboljeli od ABO liječeni u Kliničkom bolničkom centru Rijeka u razdoblju od 5 g. Ukupan broj ispitanika bio je 178, od toga 64 osoba ženskog i 114 osobe muškog spola. Prosječna dob iznosila je 74,35 ± 5,46 (65-89) godina. Svi analizirani pacijenti su se liječili kontinuiranim nadomještanjem bubrežne funkcije. Pacijenti su raspoređeni u tri skupine ovisno o ishodu bolesti, odnosno smrt, gubitak i oporavak bubrežne funkcije. Najčešće indikacije za primjenu kontinuiranog nadomještanja bubrežne funkcije bile su kardiogene etiologije (n=89, 50,0 %) te infektivne etiologije (n=52, 29,2 %). Mortalitet pacijenata oboljelih od ABO koji su bili na kontinuiranom nadomještanju bubrežne funkcije iznosi 70,79 % (n=126), dok se renalna funkcija oporavila u 6,18 % pacijenata (n=11), a 23,03 % pacijenata je moralo nastaviti jednom od metoda nadomještanja bubrežne funkcije (n=41). Analizom podataka dobiveno je da vrijednosti inicijalno mjerenog kreatinina, 24-satne diureze, glomerularne filtracije, kalija, kao i višestruko zatajenje organa, mogu biti jedan od prediktora ishoda ABO u starijih pacijenata.

Ključne riječi: **kontinuirano nadomještanje bubrežne funkcije, akutna bubrežna ozljeda, stariji, mortalitet**

VISOKODOZNA TERAPIJA PRAĆENA AUTOLOGNOM TRANSPLANTACIJOM MOŽE DOVESTI DO IZLIJEČENJA U 50 % BOLESNIKA S RELAPSNIM ILI REFRAKTORNIM HODGKINOVIM LIMFOMOM - ISKUSTVO JEDNOG CENTRA

VIBOR MILUNOVIĆ[1,2],MARTINA BOGELJIĆ PATEKAR[1], NIKOLA ZAGORAC[4], DRAŽEN PERICA[4], INGA MANDAC ROGULJ[1], IKA KARDUM-SKELIN[3], ANA PLANINC-PERAICA[1,4] i SLOBODANKA OSTOJIĆ KOLONIĆ[1,4]

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„Claire: Sometimes I hate you so much, Justine."
Lars von Trier, „Melancholia", 2011

Cilj ovog rada bio je prikazati rezultate liječenja bolesnika s relapsnim ili refraktornim klasičnim Hodgkinovim limfomom visokodoznom kemoterapijom praćenom autolognom transplantacijom matičnih stanica u jednoj ustanovi. U retrospektivno istraživanje uključen je 101 bolesnik liječen u razdoblju od 1995. do 2014. godine. Svi su bolesnici primili mijeloablativni protokol BEAM. Ukupna stopa odgovora bila je 92,1 %, medijan praćenja je iznosio 42 mjeseca. Petogodišnje ukupno preživljenje je iznosilo 56 %, a preživljenje bez progresije bolesti 51 %. U svakom ishodu postignut je plato bez daljnjih događaja pokazajući liječidbenu mogućnost ovog pristupa za oko 50 % bolesnika. Prognostički čimbenici povezani s kraćim ukupnim preživljenjem bili su prisutnost B simptoma i anemije u relapsu, odnosno nepostizanje kompletne remisije na visokodoznu terapiju. Bolesnici, koji nisu postignuli drugu kompletnu remisiju, imali su kraće ukupno preživljenje s postignutim platoom u oko 40 % bolesnika što pokazuje mogućnost autologne transplantacije da donekle umanji kemorefraktornu bolest kao negativan prognostički čimbenik. Neuspjeh postizanja druge kompletne remisije bio je jedini čimbenik povezan s kraćim preživljenjem bez progresije bolesti. Bolesnici koji nisu postignuli kompletnu remisiju na autolognu transplantaciju ili su imali drugi relaps bolesti imali su lošije petogodišnje ukupno preživljenje u iznosu od 31 % i 16 %. Prema našim rezultatima te, sukladno literaturnom pregledu, pokazali smo da je visokodozna terapija praćena autolognom transplantacijom matičnih stanica optimalan pristup ovim bolesnicima.

Ključne riječi: Hodgkinov limfom, autologna transplantacija matičnih stanica, visokodozna kemoterapija, ukupno preživljenje, prognoza

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UVOD

Klasični Hodgkinov limfom (HL) je zloćudna neoplazma B limfocitnog podrijetla s gubitkom diferencijacije B staničnih antigena (1). Karakteriziran je patognomičnim Reed-Sternbergovim i Hodgkinom stanicama koji čine manje od 1 % tumorske populacije, dok ostatak neoplazme sačinjava upalno promijenjeni mikrookoliš. Prema američkoj bazi podataka SEER incidencija HL-a iznosi 2,7 slučajeva na 100.000 stanovnika s najvećom učestalosti u mlađoj životnoj dobi, odnosno 31,5 % svih novo dijagnosticiranih HL-a pripada u dobnu skupinu između 20 i 35 godina (2). Prognoza HL-a je odlična s ukupnim petogodišnjim preživljenjem (OS prema engl. '*Overall survival*') od 79,3 % prema nedavnim podatcima EUROCARE-5 populacijske studije, odnosno većina će bolesnika biti izliječena prvom linijom terapije (3).

Bolesnici s uznapredovalom bolesti te u kojih postoje rizični faktori (Internacionalni prognostički skor, tablica 1) skloni su relapsu, odnosno 5-godišnje razdoblje bez progresije bolesti iznosi 84 % za 0 rizičnih bodova s padom do 42 % za 5 rizičnih bodova (4). Nadalje, oko 10 % bolesnika s ranom bolesti te 20 do 30 % bolesnika s uznapredovalom bolesti imat će primarno refraktornu bolest ili će doživjeti relaps (5).

Tablica 1.
Međunarodni prognostički bodovni indeks za Hodgkinov limfom (IPS)

Internacionalni Prognostički Skor*	Rizični faktori
	Dob> 45 godina
	Muški spol
	Albumini< 40 g/L
	Hemoglobin<105 g/L
	Stadij IV
	Leukociti ≥15x109/L
	Limfociti <0.6x109/L

**određuje se samo za uznapredovalu bolest*

Preporuke liječenja ovih bolesnika uključuje visokodoznu terapiju praćenu autolognom transplantacijom perifernih matičnih stanica. Ta saznanja se temelje na dva randomizirana klinička pokusa. Prvi manji BNLI klinički pokus uključivao je 40 bolesnika s relapsnim ili refraktornim HL-om (6). Ovaj mali broj bolesnika se može objasniti da je većina predviđenih bolesnika željela sudjelovati u eksperimentalnoj skupini te je stopa uključenja bila niska. Bolesnici su randomizirani u dvije skupine. Prva skupina je primila miniBEAM (karmustin, etopozid, citarabin, melfalan) kemoterapiju dok je druga skupina primila BEAM mijeloablativni protokol (karmustin, etopozid, citarabin, melfalan) praćenu reinfuzijom koštane srži. Jednogodišnje preživljenje bez događaja vezanih uz bolest (EFS prema engl. *Event Free Survival*) i preživljenje bez progresije (PFS prema engl. *Progression Free Survival*) bilo je značajno duže u transplantiranoj skupini, dok razlika u OS-u nije bila značajna zbog malog broja događaja u obje skupine (5 u BEAM skupini, 9 u miniBEAM skupini). Unatoč ovim dobrim rezultatima, sljedeće kliničko istraživanje provedeno je tek nakon desetak godina suradnjom Njemačke grupe za Hodgkinov limfom (GHSG prema engl. *German Hodgkin Study Group*) i Europskog udruženja za transplantaciju krvi i koštane srži (EBMT) (7). U ispitivanju je sudjelovao ukupno 161 bolesnik s relapsnim ili refraktornim HL-om koji su primili dva ciklusa dexaBEAM kemoterapije. U daljnju randomizaciju su uključeni samo kemosenzitivni bolesnici. Prva skupina je primila još dva ciklusa dexaBEAM kemoterapije, dok je druga skupina primila mijeloablativni BEAM protokol praćen reinfuzijom matičnih stanica. Primarni ishod pokusa bilo je vrijeme do terapijskog neuspjeha (FFTF prema engl. *Freedom of Treatment Failure*). Medijan praćenja je bio 39 mjeseci i medijan FFTF nije dosegnut u transplantiranoj skupini, a za dexaBEAM skupinu je iznosio 12 mjeseci. Također, skupine se nisu značajno razlikovale za OS koji je bio 68 % za tri godine u kemosenzitivnih bolesnika. Sustavni Cochrane pregled je potvrdio da autologna transplantacija matičnih stanica smanjuje rizik za progresiju bolesti (*hazard ratio* = 0,55) te statistički neznačajni poboljšanje OS-a (*hazard ratio* = 0,67) (8). Rezultati sustavnog pregleda imaju malu statističku snagu za dokazivanje zbog malenog broja ispitanika u navedenim kliničkim pokusima te kratkog vremena praćenja. No, unatoč nedostatku odgovarajućih dokaza, autologna transplantacija se primjenjuje u liječenju bolesnika s relapsom HL-a ili refraktornim HL-om već u devedesetim godinama prošlog stoljeća. Studija EBMT-a je uključila 139 bolesnika s HL-om transplantiranih u razdoblju od 1985. do 1993. godine (9). Petogodišnji OS je iznosio 49,4 %, a PFS 44,7 %. Mortalitet povezan s postupkom transplantacije bio je 6 %. Važno je spomenuti da je dosegnut plato u krivuljama OS-a i PFS-a te je liječenje autolognom transplantacijom učinkovito u oko 50 % bolesnika. Na temelju svih tih rezultata, visokodozna kemoterapija praćena autolognom transplantacijom čini dio dobre kliničke prakse prema preporukama svjetskih i nacionalnih smjernica u bolesnika s relapsnim ili refraktornim HL u slučaju kemosenzitivnosti osnovne bolesti (10-12).

CILJ RADA

Cilj ovog rada je prikazati rezultate liječenja autolognom transplantacijom perifernih matičnih stanica u bolesnika s relapsnom ili refraktornom HL-u. Primar-

ni ishod studije bio je OS, a sekundarni PFS. Također je učinjena analiza prognostičkih faktora povezane s ovim ishodima: dob, spol, primarno refraktorna bolest (definirana kao nepostizanje kompletne remisije na prvu liniju terapije), vrijeme do relapsa (trajanje prve kompletne remisije manje ili duže od 12 mjeseci), B simptomi pri relapsu (noćno znojenje, neobjašnjiva temperatura iznad 38° C, nenamjerni gubitak tjelesne težine za 10 % u 6 mjeseci), anemija pri relapsu (definirana kao vrijednost hemoglobina manja od 110 g/L), stadij bolesti pri relapsu (stadij I ili II, odnosno III ili IV), kemosenzitivnost (definirana kao postizanje kompletne remisije na visokodoznu terapiju) te visokodozna terapija pri relapsu.

METODE

Retrospektivno smo prikupili podatke o bolesnicima s refraktornim ili relapsnim HL-om koji su primili visokodoznu kemoterapiju praćenu autolognom transplantacijom u razdoblju od 1995. do 2014. godine u našoj ustanovi. Isključni kriteriji bili su HL-a s nodularnom limfocitnom predominacijom te progresija bolesti nakon prve linije visokodozne terapije. Istraživanje je vođeno sukladno dobroj kliničkoj praksi te su svi podatci zaštićeni sukladno Helsinškoj deklacraciji (13).

ISPITANICI

U istraživanje je uključen 101 bolesnik s relapsnim ili refraktornim HL-om liječen visokodoznom kemoterapijom praćenom autolognom transplantacijom matičnih stanica u razdoblju između 1995. i 2014. godine u našoj ustanovi. S obzirom na spolnu razdiobu, 50 ispitanika je muškog, a 51 ispitanika ženskog spola. Medijan dobi pri dijagnozi HL-a iznosio je 30 godina. Klinički podatci za bolesnike na početku praćenja prikazani su u tablici 2.

Tablica 2.
Osnovne karakteristike bolesnika pri dijagnozi

Karakteristike bolesnika		
Spol	M 46,5 %	Ž 53,5 %
Dob pri dijagnozi	30	
Klinički stadij po Ann Arbour14	I/II 52,8 %	III/IV 48,2 %
Stadij bolesti po GHSG15	Rani, povoljan 12,5 %	
	Rani, nepovoljan 17,0 %	
	Uznapredovala bolest 70 %	
Prisutnost B simptoma*	52,8 %	
Ekstranodalna bolest	14,8 %	
"Bulky" bolest**	33 %	
IPS	2	
Prva linija terapije	ABVD 63,9 %***	
	MOPP-ABV 24,7 %****	
	Ostalo 11,4 %	
Zračenje	27,8 %	
Odgovor	Kompletna/parcijalna remisija 75,3 %	
	Stabilna bolest/progresija 24,7 %	

*B simptomi: noćno znojenje, febrilitet iznad 38°C, gubitak tjelesene težine veći od 10 % u 6 mjeseci
**"Bulky" bolest je definirana kao tumorska masa veća od 6 cm
***ABVD- doksorubicin, bleomicin, vinblastin, dakarbazin,
****MOPP-ABV-mekloretamin, vinkristin, prokarbazin, prednison, doksorubicin, bleomicin, vinblastin

Medijan vremena od dijagnoze do autologne transplantacije matičnih stanica iznosio je 19 mjeseci. Medijan dobi pri autolognoj transplantaciji matičnih stanica iznosio je 31 godina. U 60,4 % bolesnika učinjena je autologna transplantacija u razdoblju između 1995. i 2003. godine. Najčešće korištena visokodozna kemoterapija bila je shema miniBEAM. Klinički podatci bolesnika prije autologne transplantacije prikazane su u tablici 3.

Tablica 3.
Karakteristike bolesnika pri autolognoj transplantaciji matičnih stanica

Dob	31	
Razdoblje	1995-2003. 60,4 %	
	2004-2014. 39,6 %	
Klinički stadij pri relapsu	I/II 53,5 %	III/IV 46,5 %
Anemija pri relapsu	23,8 %	
B simptomi pri relapsu	34,5 %	
Rani relaps*	30,2 %	
Vrsta visokodozne terapije	miniBEAM 49,5 %	
	BEACOPP** 17,6 %	
	Ostalo 31,9 %	
Kompletna ili parcijalna remisija nakon visokodozne terapije	67,9 %	

*rani relaps je definiran kao relaps između 3 i 12 mjeseci nakon završene prve linije terapije

**BEACOPP-bleomicin, etopozid, doksorubicin, ciklofosfamid, vinkristin, prokarbazin, prednizon

Odgovor na visokodoznu terapiju procijenjen je ultrazvukom površinskih regija limfnih čvorova i abdomena, RTG-om srca i pluća te citološkom punkcijom koštane srži u slučaju prijašnje infiltracije. Većina bolesnika je postigla kompletnu ili parcijalnu remisiju (67,9 %). Bolesnici u kojih je došlo do pogoršanja nakon prve linije visokodozne kemoterapije bili su isključeni iz studije. U svih je bolesnika primijenjena mijeloablativna shema BEAM praćena reinfuzijom matičnih stanica. Odgovor na autolognu transplantaciju matičnih stanica bio je klinički procijenjen mjesec dana nakon otpusta iz bolnice. U većine bolesnika je učinak liječenja procijenjen na temelju ultrazvuka površinskih regija limfnih čvorova i abdomena, RTG slike srca i pluća, te pozitronske emisijske tomografije s kompjuteriziranom tomografijom kad je to bilo moguće.

STATISTIČKA ANALIZA

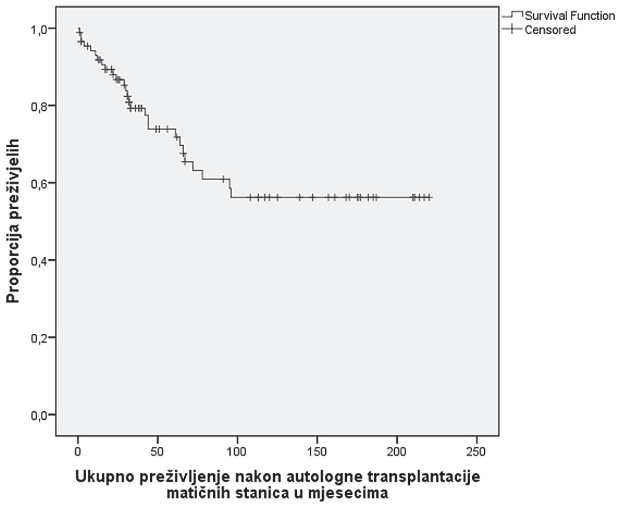
Podatci su prikazani deskriptivnom statistikom, te analizirani po metodi Kaplan-Meier za ishode te tablice života. U analizi prognostičkih čimbenika korišten je log-rank test. Statističkim značajnim rezultatima bili su smatrani oni rezultati s p vrijednosti manjom od 0,05. Sve analize su učinjene pomoću statističkog programa *Statistical Package for Social Sciences* verzija 20.0 (IBM) (16).

REZULTATI

Odgovor na autolognu transplantaciju matičnih stanica i ukupno preživljenje

Ukupni odgovor (ORR prema engl. *Overall Reponse Rate*) na mijeloablativnu terapiju po shemi BEAM praćenu autolognom transplantacijom matičnih stanica iznosio je 92,1 %. Od toga je bilo ukupno 76,2 % kompletnih remisija te 15,8 % parcijalnih remisija.

Medijan praćenja bolesnika bio je 42 mjeseca. Medijan OS-a (izračunat od datuma autologne transplantacije do datuma smrti ili zadnje kontrole) nije dosegnut te je 56,2 % bolesnika bilo živo nakon 96 mjeseci praćenja s postignutim platoom bez daljnjih događaja (sl. 1). Ukupna stopa 5-godišnjeg OS-a iznosila je 56 %.

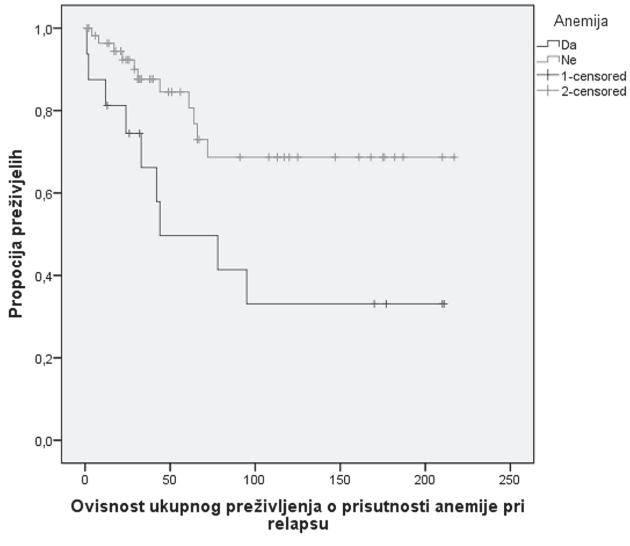


Sl. 1. *Ukupno preživljenje nakon visokodozne terapije praćene autolognom transplantacijom matičnih stanica izraženo u mjesecima. Prognostički čimbenici ukupnog preživljenja nakon autologne transplantacije matičnih stanica*

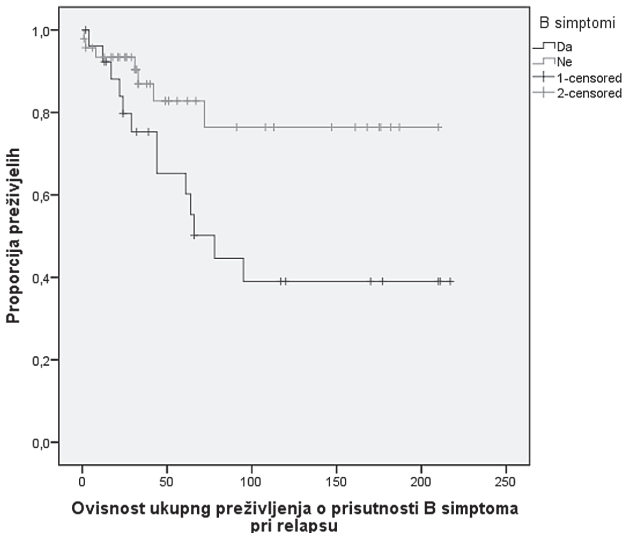
Kao jedan od mogućih čimbenika analizirali smo spolnu razdiobu. Nije bilo statistički značajne razlike u OS-u s obzirom na spol (p=0,894). Pri analizi za dobne skupine, kao vrijednost starije životne dobi uzeli smo 45 godine starosti ili više prema IPS bodovnom indeksu (4). Razlika nije bila statički značajna (p=0,272). Treći ispitivani čimbenik su bile godine kada je provedena autologna transplantacija matičnih stanica. Bolesnici su bili podijeljeni u dvije skupine. Prva skupina je transplantirana u razdoblju između 1995. i 2003. godine, dok je u drugoj skupini autologna transplantacija učinjena u razdoblju između 2004. i 2014. godine (vidljivo na tablici 3.). Razlika u preživljenju nije bila statički značajna (p=0,902).

S obzirom na rizične faktore analizirali smo kemorefraktornu bolest pri prvoj liniji terapije, prisutnost anemije pri relapsu, pisutnost B simptoma pri relapsu, klinički stadij po Ann Arbor klasifikaciji pri relapsu, rani relaps, kemosenzitivnost bolesti te vrstu visokodozne terapija.

U analizi OS-a kemorefraktorna bolest se nije pokazala statistički značajnim prognostičkim čimbenikom (p=0,529). Prisutnost anemije pri relapsu je statistički značajan čimbenik. Bolesnici, koji su imali anemiju, imali su značajno manji OS (medijan OS-a= 44 mjeseca) za razliku od bolesnika bez anemije u kojih medijan nije dosegnut što je prikazano na sl. 2. (p = 0,012). Prisutnost B simptoma pri relapsu također je bio statistički značajan prognostički čimbenik (p=0,02). Bolesnici s izraženim B simptomima imali su medijan OS-a u iznosu od 78 mjeseci za razliku od bolesnika bez izraženih B simptoma u kojih medijan nije dosegnut (sl. 3). U daljnoj analizi podijelili smo bolesnike prema kliničkom stadiju određenom po Cotswaldovoj modifikaciji Ann Arbor klasifikacije (14). Razlika u OS-u, s obzirom na klinički stadij nije bila statički značajna (p=0,592).Rani relaps nije bio povezan sa značajnom razlikom u OS-u (p=0,397). Bolesnici s drugom kompletnom remisijom nakon visokodozne terapije imali su značajno duži OS (medijan nije dosegnut) za razliku od ostalih bolesnika u kojih je medijan OS-a iznosio 95 mjeseci (p=0,023). (sl. 4). S obzirom na mogući „bias“ te činjenicu da pojedini istraživači smatraju i parcijalnu remisiju kao znak kemosenzitivne bolesti, u daljnju smo analizu uključili i bolesnike s parcijalnom remisijom te je razlika i dalje ostala statistički značajna (11,12). Kao što je vidljivo na sl. 4. postignut je plato u OS-u nakon autologne transplantacije u oko 40 % kemorefraktornih bolesnika.

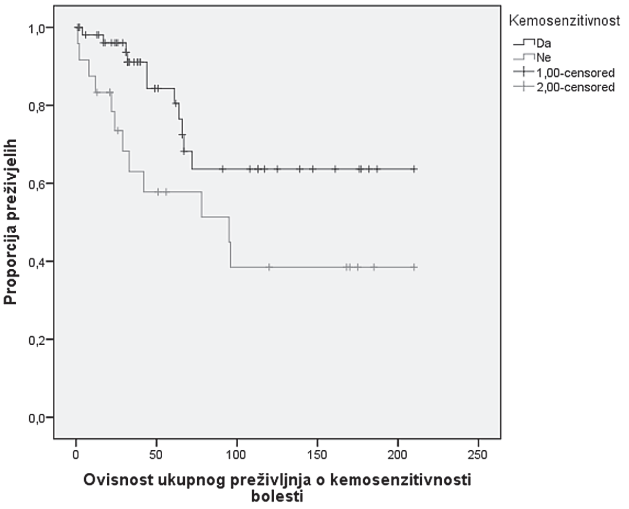


Sl. 2. *Ovisnost ukupnog preživljenja nakon autologne transplantacije matičnih stanica o prisutnosti anemiji (hemoglobin manji od 110 g/L) pri relapsu*



Sl. 3. *Ovisnost ukupnog preživljenja nakon autologne transplantacije matičnih stanica o prisutnosti B simptoma**

**(B simptomi su definirani kao prisutnost jednog ili više kliničkih fenomena; noćno znojenje, neobjašnjiva tjelesna temperatura veća od 38°C te nenamjeran gubitak tjelesne težine veći od 10 % u razdoblju od 6 mjeseci*



Sl. 4. *Kemosenzitivost kao prognostički čimbenik ukupnog preživljenja pri autolognoj transplantaciji matičnih stanica**

**kemosenzitivnost je definirana kao postizanje kompletne remisije nakon visokodozne terapije*

S obzirom da je visokodozna kemoterapija po shemi miniBEAM bila najčešće (49,5 %) korištena terapija u ovih bolesnika, bolesnike smo podijelili u dvije skupine. Prva skupina je primila kemoterapiju po shemi miniBEAM, dok je druga skupina primila neki od drugih modaliteta visokodozne kemoterapije. Ta razlika nije bila statički značajna u OS-u te je srednji OS bio podjednak u obe skupine (p=0,807).

Kao posljednji prognostički čimbenik analizirali smo odgovor na autolognu transplantaciju matičnih stanica. U bolesnika u kojih je postignuta kompletna re-

misija medijan OS-a nije dosegnut za razliku od parcijalne remisije (medijan 44 mjeseci), stabilne bolesti (29 mjeseci), odnosno progresije bolesti (medijan 2 mjeseca). Ta razlika je statistički značajna (p<0,001). Stopa 5-godišnjeg preživljenja iznosila je 31 % za bolesnike koji nisu postignuli kompletnu remisiju kao odgovor na autolognu transplantaciju matičnih stanica.

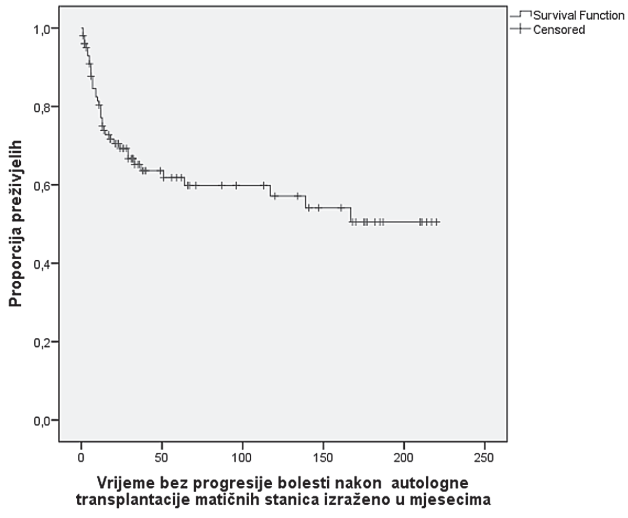
Svi navedeni rezultati prikazani su u tablici 4.

Tablica 4.
Analiza mogućih čimbenika povezanih s ukupnim preživljenjem nakon autologne transplantacije matičnih stanica pomoću log-rank testa

Čimbenik	χ^2	df	p
Spol	0,018	1	0,894
Dob iznad 45 godina	1,200	1	0,272
Razdoblje	0,015	1	0,902
Primarno kemorefraktorna bolest	0,397	1	0,592
Anemija	6,424	1	0,012
B simptomi	5,370	1	0,020
Klinički stadij	0,397	1	0,592
Rani relaps	0,717	1	0,397
Kemosenzitivnost	5,132	1	0,023
miniBEAM	0,060	1	0,807
Odgovor na autolognu transplantaciju	39,233	3	<0,001

Vrijeme bez progresije bolesti i prognostički čimbenici

Medijan PFS-a (računato od datuma autologne transplantacije do relapsa ili zadnje kontrole) u ovoj skupini bolesnika nije dosegnut, odnosno 50,5 % bolesnika nije doživjelo relaps osnovne bolesti nakon 167 mjeseci praćenja s postignutim platoom (sl. 5). Petogodišnji PFS iznosio je 51 %.



Sl. 5. *Vrijeme bez progresije bolesti nakon autologne transplantacije matičnih stanica*

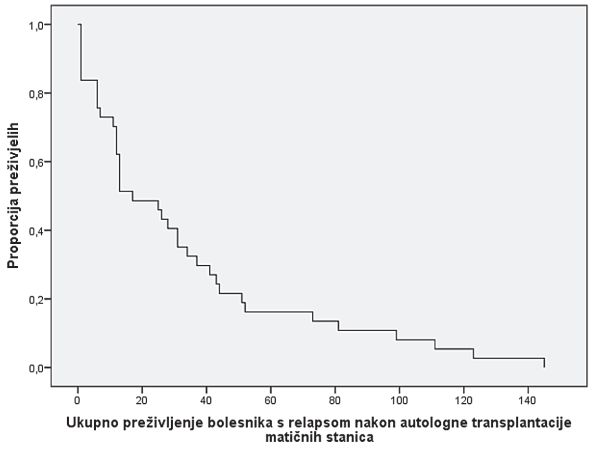
Kemosenzitivnost bolesti prije autologne transplantacije bio je jedini statistički značajni čimbenik. Medijan PFS-a kemorefraktornih bolesnika iznosio je 29 mjeseci dok nije dosegnut u kemosenzitivnih bolesnika (p=0,036). Ostali čimbenici nisu bili statistički značajni; spol (p=0,81), dob pri autolognoj transplantaciji (p=0,704), vremensko razdoblje autologne transplantacije (p=0,762), primarno kemorefraktorna bolest (p=0,606), klinički stadij pri relapsu (p=0,518), prisutnost anemije (p=0,653), prisutnost B simptoma (p=0,112), rani relaps (p=0,108) te upotreba miniBEAM visokodozne terapije (p=0,81). Svi navedeni rezultati su prikazani u tablici 5.

Tablica 5.
Analiza mogućih čimbenika povezanih s vremenom bez progresije bolesti nakon autologne transplantacije matičnih stanica pomoću log-rank testa

Čimbenik	χ2	df	p
Spol	0,058	1	0,810
Dob	0,144	1	0,704
Razdoblje	0,092	1	0,762
Primarno kemorefraktorna bolest	0,265	1	0,606
Klinički stadij	0,418	1	0,518
Anemija	0,853	2	0,653
B simptomi	2,522	1	0,112
Rani relaps	2,590	1	0,108
Kemosenzitivnost	4,413	1	0,036
miniBEAM	0,058	1	0,810

Ishod bolesnika s relapsom nakon autologne transplantacije matičnih stanica

Tijekom praćenja nakon autologne transplantacije, 37 bolesnika je doživjelo relaps. Medijan OS-a ovih bolesnika iznosio je 17 mjeseci, dok je 5-godišnji OS bio 16 % (sl. 6). Važno je istaknuti da je 29,7 % bolesnika s relapsom živjelo dulje od tri godine.



Sl. 6. *Ukupno preživljenje bolesnika koji su doživjeli relaps nakon autologne transplantacije matičnih stanica*

RASPRAVA

Ishodi autologne transplantacije matičnih stanica u relapsnom ili refraktornom Hodgkinovom limfomu

Najvažni rezultat naše studije je da je dosegnut plato bez relapsa nakon vremena praćenja od 167 mjeseci ili smrti nakon vremena praćenja od 96 mjeseci, a što ukazuje da je u ovoj skupini bolesnika visokodozna kemoterapija praćena autolognom transplantacijom matičnih stanica učinkovita u 50 % bolesnika s relapsnim ili refraktornim HL-om. Medijan OS-a nije postignut i 56,2 % bolesnika je bilo živo nakon 96 mjeseci praćenja. Također, medijan za PFS nije dosegnut te je 50,5 % bolesnika bilo bez znakova bolesti nakon 167 mjeseci praćenja. Stopa 5- godišnjeg OS-a iznosila je 56 % dok je za PFS iznosila 51 %, što pokazuje da autologna transplantacija može predstavljati liječidbenu opciju u ovom kliničkom okružju. Naši rezultati su usporedivi s rezultatima talijanske skupine autora koja je pokazala 10-godišnji OS od 57 % te PFS od 51 % u svojoj skupini bolesnika (1). Prema literaturnom pregledu rezultate s najduljim praćenjem (medijan praćenja 10 godina) pokazala je britanska skupina na 119 bolesnika (18). Petogodišnja stopa OS-a iznosila je 55 % sa stopom PFS-a u vrijednosti od 44 %. U ovoj studiji je 20 bolesnika razvilo sekundarnu neoplazmu, od toga sedmoro akutnu mijeloičnu leukemiju ili mijelodisplastični sindrom sa 10 godišnjim rizikom od 7 % za hematološke neoplazme. U naših bolesnika je zabilježen samo jedan slučaj mijelodisplastičnog sindroma sa smrtnim ishodom, dok za sekundarne solidne neoplazme nismo prikupljali podatke.

BEAM mijeloablativna terapija

Naši rezultati ukazuju na visoki ORR (92,1 %) na BEAM mijeloablativnu terapiju praćenu transplantacijom matičnih stanica. Ti su rezultati sukladni rezultatima Argirisa i sur. koji su pokazali stopu kompletnih remisija na navedenu mijeloablativnu terapiju u HL u iznosu od 92 % (19). Druga retrospektivna studija je uključila 155 bolesnika s primarno refraktornim ili relapsnim HL-om liječenim BEAM mijeloablativnim protokolom (20). U ovih bolesnika ORR je iznosio 74 % s većinom parcijalnih odgovora (46 %). Lošiji ishod je vjerojatno posljedica nepovoljnih rizičnih čimbenika bolesti uključenih bolesnika, tj. postojanja više rizičnih faktora. Nedavna retrospektivna studija je ispitivala različite mijeloablativne protokole u malignim limfomima, odnosno u studiju je bilo uključeno 1012 bolesnika s HL-om (21). BEAM kemoterapija uz kemoterapiju po shemi CBV (ciklofosfamid, karmustin, etopozid) pokazala je prednost u obliku 3 godišnjeg OS-a u iznosu od 79 % te stope relapsa u iznosu od 32 %. Nadalje, BEAM je bio superioran što tiče mortaliteta vezanog uz liječenje (TRM prema engl. *Treatment-Related Mortality*) prema svim ostalim protokolima. TRM za BEAM iznosio je 4 %. Ako ekstrapoliramo naše podatke kao smrtnost u prvih godinu dana kao TRM, za našu skupinu bolesnika TRM je iznosio 9,2 %. Nadalje, u direktnoj usporedbi s CBV kemoterapijom, nedavna retrospektivna skupina iz registra Nebraske na 225 živućih autotransplantiranih bolesnika s HL-om je pokazala bolji 5-godišnji OS od 95 % te PFS od 73 % za BEAM skupinu (22). Bitno je naglasiti da je analiza uključivala samo žive bolesnike bez znakova bolesti. S obzirom na niski TRM, odnosno pokazanu veću učinkovitost naspram drugih mijeloablativnih protokola, BEAM mijeloablativni protokol je, sukladno našim rezultatima, postao vodeći protokol u ovom kliničkom okruženju premda vodeće svjetskle smjernice zbog nedostatka randomiziranih pokusa ne preporučuju specifični mijeloablativni protokol (10,11).

MiniBEAM kao visokodozna terapija

U polovice naših bolesnika korištena je visokodozna kemoterapija po shemi miniBEAM. U daljnjoj analizi nismo našli razliku u OS-u i PFS-u s obzirom na korištenje miniBEAM terapije, no moramo istaknuti mogući „bias" u analizi s obzirom na heterogenost ostalih doza kemoterapije. Ukupni ORR na miniBEAM prema retrospektivnoj studiji Martina i sur. iznosio je 84 %, no uz značajnu toksičnost, primarno mijelosupresiju (86 %) te infekcije (61 %) (23). Posljedično je ovaj protokol rjeđe primjenjivan, osobito nakon razvoja novih protokola, primjerice ICE (ifosfamid, carboplatin, etopozid) i DHAP (cisplatin, citarabin dexametazon) (24,25).

Prognostički čimbenici povezani s ishodom autologne transplantacije matičnih stanica u relapsnom ili refraktrornom Hodgkinovom limfomu

Čimbenici lošeg prognostičnog ishoda su u ovom istraživanju bili: B simptomi i anemija pri relapsu, te kemorefrakternost bolesti na visokodoznu terapiju. Kemorefraktorna bolest na visokodoznu terapiju bila je jedini čimbenik povezan s lošijim PFS-om. Njemačka GHSG skupina je razvila prognostički indeks na 422 bolesnika s HL-om podvrgnutih autolognoj transplantaciji matičnih stanica (27). U analizi su utvrdili 5 karakteristika povezanih s lošijim ishodom: vrijeme do relapsa, klinički stadij, prisutnost anemije, abnormalne vrijednosti sedimentacije i alkalne fosfataze. U daljnoj analizi su koristili anemiju, klinički stadij te vrijeme do relapsa (kraće od 12 mjeseci) te razvrstali bolesnike u 4 skupine na temelju OS-a i FFTF-a. Prema našim rezultatima jedino se anemija pokazala značajnom u predikciji lošeg ishoda, ali ne i klinički stadij u relapsu. Za procjenu kliničkog stadija smo ponajprije koristili ultrazvuk koji ima manju osjetljivost

od PET-CT. To su objektivne poteškoće retrospektivne studije. Usprkos ravnomjernoj podjeli frekvencija kliničkog stadija pri relapsu prikazih u tablici 2, nismo našli statistički značajnu razliku. Razlog može biti razvrstavanje bolesnika, tj. „*upstaging*" i „*downstaging*" na temelju ultrazvučne metode, a ne CT-a odnosno PET-CT-a prema preporukama kriterija za odgovor u malignim limfomima iz 1998. i 2007. godine (28,29). Budući da je ovo retrospektivna studija, to je ujedno i ograničenje istraživanja. Moramo naglasiti da je osjetljivost ultrazvuka u dijagnozi HL 60-70 %, specifičnost veća od 90 %, a što ga je činilo prihvatljivim dijagnostičkim sredstvom u prošlosti (30).

Rani relaps (3-12 mjeseci od završetka prve linije kemoterapije) nije bio povezan s lošim ishodom autologne transplantacije matičnih stanica, usprkos što ga većina studija definira kao nepovoljan prognostički čimbenik (27,31,32). Za naše istraživanje to je vjerojatno posljedica malog broja slučajeva ranog relapsa te analize vremena relapsa kao dihotomne, a ne kontinuirane varijable u statističkoj analizi.

Kao jedan od čimbenika povezan s lošijom prognozom bila je i prisutnost sustavnih B simptoma pri relapsu. Prema literaturnom pregledu, Martin i sur. su u svojoj analizi 55 bolesnika s relapsnim i refraktornim HL-om odredili prisutnost B simptoma kao negativni prognostički čimbenik u bolesnika liječenih miniBEAM kemoterapijom (23). Nadalje, američka skupina iz *Memorial Sloan Kettering Cancer Centre* odredila je prisutnost B simptoma kao neovisni prognostički čimbenik za bolesnike liječene visokodoznom kemoterapijom po shemi ICE (33).

Kemorefraktornost bolesti na visokodoznu terapiju je čimbenik povezan s oba ishoda naše studije. EBMT skupina je pokazala u 139 bolesnika s refraktornim ili relapsnim HL-om da je druga kompletna remisija neovisni prognostički čimbenik OS-a, sukladno našem istraživanju, budući da je za nas definicija kemosenzitivnosti bilo postizanje druge kompletne remisije (9). Također, francuska skupina je odredila kemosenzitivni relaps na 280 bolesnika kao prediktor boljeg OS-a (34). Važan rezultat je postizanje platoa u OS-u u kemorezistentne skupine za oko 40 % bolesnika (sl. 4) autolognom transplantacijom matičnih stanica u bolesnika u kojih nije ostvarena druga kompletna remisija.

Na to pitanje je pokušala odgovoriti skupina Britanske Kolumbije u svoj analizi 256 primarno refraktornih ili relapsnih HL bolesnika (35). Nakon medijana praćenja od 11,7 godina, 10-godišnja stopa OS-a za primarno refraktorne bolesnike, koji nisu odgovorili na visokodoznu kemoterapiju, bila je 29 %, dok je za kemorefraktorne bolesnike u relapsu bila 59 %. U multivarijatnoj analizi kemorezistentnost na visokodoznu kemoterapiju nije imala utjecaj na FFS u obje skupine te utjecaj na OS u relapsnoj skupini. Autori zaključuju da autologna transplantacija može biti dobar izbor liječenja i za kemorefraktorne bolesnike zbog parcijalnog nadvladavanja kemorezistencije što rezultira izlječenjem između 30 i 50 % bolesnika. Na tragu tog stava je i naše iskustvo, unatoč postojećih smjernica koje preporučuju ovaj postupak samo u kemosenzitivnih bolesnika (10-12).

Neočekivani rezultat je podudarnost u preživljenju između primarno refraktornih bolesnika i bolesnika u relapsu. Primarna kemofraktorna bolest se tradicionalno smatra visoko rizičnom skupinom u HL-u na temelju različitih studija (36).

Prema literaturnom pregledu, najveće iskustvo dolazi iz GHSG retrospektivne analize koja je uključivala 206 primarno refraktornih bolesnika (37). Petogodišnja stopa OS-a iznosila je 26 %, dok je 17 % bolesnika bilo bez znakova bolesti. Kao najčešći modalitet terapije korištena je visokodozna terapija, a u 33 % bolesnika je učinjena autologna transplantacija što može objasniti ovu lošu prognozu. EBMT iskustvo na 175 primarno refraktornih bolesnika je pokazalo da autologna transplantacija matičnih stanica dovodi do određene kontrole bolesti, odnosno 5-godišnja stopa OS-a je 36 % dok za PFS iznosi 32 % (38). U našoj je studiji bilo malo bolesnika s primarno refraktornom bolesti, a što je vrlo vjerojatno utjecalo na ovaj ishod.

Kao odgovor na problem heterogenosti prognostičkih čimbenika u različitim studijama u ovom kliničkom okružju, Društvo za proučavanje limfoma (*Lymphoma Study Association*, LYSA) je definiralo preporuke o stratifikaciji i zbrinjavanju bolesnika s relapsnim ili refraktornim HL-a (39). Kao rizični čimbenici odabrani su primarno refraktorna bolest, rani relaps te stadij III ili IV pri relapsu.

S obzirom da odabir ovih čimbenika nije proizašao kao rezultat sustavnog pregleda, smatramo da su potrebna prospektivna istraživanja koja će validirati ove čimbenike i pristup LYSA skupine bolesnicima s HL-om pogodnim za autolognu transplantaciju matičnih stanica.

Ishod bolesnika koji nisu odgovorili na liječenje ili su doživjeli relaps nakon autologne transplantacije matičnih stanica

Ukupno 5-godišnje preživljenje bolesnika, koji nisu postignuli kompletnu remisiju na autolognu transplantaciju matičnih stanica, iznosilo je 31 %. Za bolesnike, koji su doživjeli drugi relaps, 5-godišnji OS iznosio je 16 %. Ovi podatci ukazuju na vrlo lošu prognozu u bolesnika u kojih autologna transplantacija

matičnih stanica nije uspjela. Najveće iskustvo u ovih bolesnika prikazala je EBMT skupina (40). Medijan OS-a iznosio je 29 mjeseci uz 5-godišnju stopu OS-a od 32 % što je više nego u našoj seriji. Ta bi se razlika mogla objasniti s primjenom alogeneične terapije EBMT skupini, odnosno 29 % njihove kohorte bilo je alotransplantirano. U našoj kohorti broj alotransplantiranih bolesnika je gotovo mali.

Liječenje ovih bolesnika je vrlo složeno. Terapijske se odluke donose na temelju općeg zdravstvenog statusa bolesnika te variraju od monoterapije vinblastinom ili gemcitabinom, visokodozne kemoterapije temeljene na gemcitabinu do alogenične transplantacije matičnih stanica (41). Nove mogućnosti liječenja uključuju brentuksimab vedotin, antiCD30 imunokonjugirano protutijelo. Za liječenje brentuksimab vedotinom su ishodi (PFS) bili bolji u odnosu na konvencionalnu kemoterapiju u bolesnika s relapsnim ili refraktornim HL-om nakon autologne transplantacije (42,43). U Hrvatskoj je brentuksimab vedotin odobren za liječenja relapsnog ili refaktornog HL-a nakon autologne transplantacije matičnih stanica odnosno HL-a u kojem autologna transplantacija nije opcija (44,45).

LIMITACIJE

Limitacije ove studije su inherentne svakoj studiji retrospektivne naravi, odnosno heterogenost podataka, zbog dugog razdoblja i različitosti pristupa, otežava analizu. Jedna od limitacija je što se nisu koristili kriteriji za odgovor u liječenju malignih limfoma što može interferirati s preciznošću naših podataka, no kako ova studija nije klinički pokus, nego pokazatelj rutinske kliničke prakse jednog centra ta limitacija ne ugrožava interpretaciju rezultata (28,29). Druga limitacija leži u činjenici da u statističkoj analizi nismo koristili multivarijatnu analizu, no zbog malog broja događaja u studiji premisa takve analize ne bi bila opravdana (46).

ZAKLJUČAK

U ovoj studiji je liječenje visokodoznom terapijom i autolognom transplantacijom matičnih stanica imalo dobar ishod u polovice bolesnika s relapsnim ili refraktornim HL. Prognostički čimbenici nepovoljnog ishoda bili su anemije, B simptomi pri relapsu odnosno kemorefraktornosti bolesti na visokodoznu terapiju. Rezultati našeg istraživanja su podudarni s većinom suvremenih saznanja liječenja ovih bolesnika.

L I T E R A T U R A

1. Swerdlow SH, Campo E, Harris NL i sur. WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues (ed 4th). Lyon, France: IARC Press; 2008.

2. Surveillance, Epidemiology and End Results Program. SEER Stat Fact Sheets: Hodgkin lymphoma. Dostupno na URL adresi: http://seer.cancer.gov/statfacts/html/hodg.html Datum pristupa informaciji 11/12/2015 godine

3. Sant M, Minicozzi P, Mounier M i sur. Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: results of EUROCARE-5, a population-based study. Lancet Oncol 2014; 15: 931-42.

4. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 1998; 339: 1506-14.

5. Townsend W, Linch D. Hodgkin's lymphoma in adults. Lancet 2012; 380: 836-47.

6. Linch DC, Winfield D, Goldstone AH i sur. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet 1993; 341: 1051-4.

7. Schmitz N, Pfistner B, Sextro M i sur. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. Lancet 2002; 359: 2065-71.

8. Rancea M, Monsef I, von Tresckow B, Engert A, Skoetz N. High-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed/refractory Hodgkin lymphoma. Cochrane Database Syst Rev 2013; 6: CD009411.

9. Sweetenham JW, Taghipour G, Milligan D i sur. High-dose therapy and autologous stem cell rescue for patients with Hodgkin's disease in first relapse after chemotherapy: results from the EBMT. Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 1997; 20: 745-52.

10. Eichenauer DA, Engert A, André M i sur. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014 ;25 (Supl 3): iii70-5.

11. Hoppe RT, Advani RH i sur. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Hodgkin lymphoma Version 2.2015 Dostupno na URL adresi: http://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf Datum pristupa informaciji: 10/12/2015.

12. Aurer I, Gasparov S, Kralik M i sur. [Lymphoma diagnosis and treatment - second Croatian consensus]. Lijec Vjesn 2013; 135: 63-76.

13. World Medical Association. WMA Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects. 64th WMA General Assembly, Fortaleza, Brazil, October 2013 dostupno na URL adresi: http://www.wma.net/en/30publications/10policies/b3/ Datum pristupa informaciji 10/12/2015.

14. Lister TA, Crowther D, Sutcliffe SB i sur. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989; 7:1630-6.

15. German Hodgkin Study Group. Risk Groups dostupno na URL adresi: http://en.ghsg.org/risk-groups Datum pristupa infromaciji: 10/12/2015

16. IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

17. Viviani S, Di Nicola M, Bonfante V i sur. Long-term results of high-dose chemotherapy with autologous bone marrow or peripheral stem cell transplant as first salvage treatment for relapsed or refractory Hodgkin lymphoma: a single institution experience. Leuk Lymphoma 2010; 51: 1251-9.

18. Sirohi B, Cunningham D, Powles R i sur. Long-term outcome of autologous stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma. Ann Oncol 2008; 19: 1312-9.

19. Argiris A, Seropian S, Cooper DL. High-dose BEAM chemotherapy with autologous peripheral blood progenitor-cell transplantation for unselected patients with primary refractory or relapsed Hodgkin's disease. Ann Oncol 2000; 11: 665-72.

20. Chopra R, McMillan AK, Linch DC i sur. The place of high-dose BEAM therapy and autologous bone marrow transplantation in poor-risk Hodgkin's disease. A single-center eight-year study of 155 patients. Blood 1993; 81: 1137-45.

21. Chen YB, Lane AA, Logan BR i sur. Impact of conditioning regimen on outcomes for patients with lymphoma undergoing high-dose therapy with autologous hematopoietic cell transplantation. Biol Blood Marrow Transplant 2015; 21: 1046-53.

22. William BM, Loberiza FR Jr, Whalen V i sur. Impact of conditioning regimen on outcome of 2-year disease-free survivors of autologous stem cell transplantation for Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk 2013; 13: 417-23.

23. Martín A, Fernández-Jiménez MC, Caballero MD i sur. Long-term follow-up in patients treated with Mini-BEAM as salvage therapy for relapsed or refractory Hodgkin's disease. Br J Haematol 2001; 113: 161-71.

24. Moskowitz CH, Bertino JR, Glassman JR i sur. Fosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. J Clin Oncol 1999; 17: 3776-85.

25. Josting A, Rudolph C, Reiser M i sur. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. Ann Oncol 2002; 13: 1628-35.

26. Mendler JH, Friedberg JW. Salvage therapy in Hodgkin's lymphoma. Oncologist 2009; 14: 425-32.

27. Josting A, Franklin J, May M i sur. New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German Hodgkin's lymphoma study group. J Clin Oncol 2002; 20: 221-30.

28. Cheson BD, Horning SJ, Coiffier B i sur. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999; 17: 1244.

29. Cheson BD, Pfistner B, Juweid ME i sur. Revised response criteria for malignant lymphoma. J Clin Oncol 2007; 25: 579-86.

30. Rochester D, Bowie JD, Kunzmann A, Lester E. Ultrasound in the staging of lymphoma. Radiology 1977; 124: 483-7.

31. Martínez C, Canals C, Sarina B i sur. Identification of prognostic factors predicting outcome in Hodgkin's lymphoma patients relapsing after autologous stem cell transplantation. Ann Oncol 2013; 24: 2430-4.

32. Sureda A, Constans M, Iriondo A i sur. Prognostic factors affecting long-term outcome after stem cell transplantation in Hodgkin's lymphoma autografted after a first relapse. Ann Oncol 2005; 16: 625-33.

33. Moskowitz CH, Nimer SD, Zelenetz AD i sur. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. Blood 2001; 97: 616-23.

34. Brice P, Bouabdallah R, Moreau P i sur. Prognostic factors for survival after high-dose therapy and autologous stem cell transplantation for patients with relapsing Hodgkin's disease: analysis of 280 patients from the French registry. Société Française de Greffe de Moëlle. Bone Marrow Transplant 1997; 20: 21-6.

35. Gerrie AS, Power MM, Shepherd JD, Savage KJ, Sehn LH, Connors JM. Chemoresistance can be overcome with high-dose chemotherapy and autologous stem-cell transplantation for relapsed and refractory Hodgkin lymphoma. Ann Oncol 2014; 25: 2218-23.

36. Castagna L, Carlo-Stella C, Mazza R, Santoro A. Current role of autologous and allogeneic stem cell transplantation for relapsed and refractory Hodgkin lymphoma. Mediterr J Hematol Infect Dis 2015; 7: e2015015.

37. Josting A, Rueffer U, Franklin J, Sieber M, Diehl V, Engert A. Prognostic factors and treatment outcome in primary progressive Hodgkin lymphoma: a report from the German Hodgkin Lymphoma Study Group. Blood 2000; 96: 1280-6.

38. Sweetenham JW, Carella AM, Taghipour G i sur. High-dose therapy and autologous stem-cell transplantation for adult patients with Hodgkin's disease who do not enter remission after induction chemotherapy: results in 175 patients reported to the European Group for Blood and Marrow Transplantation. Lymphoma Working Party. J Clin Oncol 1999; 17: 3101-9.

39. Van Den Neste E, Casasnovas O, André M i sur. Classical Hodgkin's lymphoma: the Lymphoma Study Association guidelines for relapsed and refractory adult patients eligible for transplant. Haematologica 2013; 98: 1185-9.5

40. Martínez C, Canals C, Sarina B i sur. Identification of prognostic factors predicting outcome in Hodgkin's lymphoma patients relapsing after autologous stem cell transplantation. Ann Oncol 2013; 24: 2430-4.

41. Kuruvilla J, Keating A, Crump M. How I treat relapsed and refractory Hodgkin lymphoma. Blood 2011; 117: 4208-17.

42. Younes A, Gopal AK, Smith SE i sur. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol 2012; 30: 2183-9.

43. Moskowitz CH, Nademanee A, Masszi T i sur. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015; 385: 1853-62.

44. Hrvatski zavod za zdravstveno osiguranje. Odluka o utvrđivanju popisa posebno skupih lijekova utvrđenom odlukom o utvrđvanju osnovne liste lijekova Hrvatskog zavoda za zdravstveno osiguranje datum odluke 23.10. 2015 dostupno na URL adresi: http://www.propisi.hr/print.php?id=4920 datum pristupa informaciji 17/12/2015

45. European Medicines Agency. Adcetris. Brentuximab Vedotin. Product Information. Dostupno na URL adresi: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002455/WC500135055.pdf datum pristupa informaciji 17/12/2015

46. Stamhuis IH, Bezemer PD, Kuik DJ. Evaluation of univariate ranges with a multivariate standard. J Clin Epidemiol 1988; 41: 359-66.

SUMMARY

SALVAGE CHEMOTHERAPY FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION MAY BE CURATIVE IN 50% OF RELAPSED OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA: A SINGLE-CENTER EXPERIENCE

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The main aim of this study was to present outcomes and prognostic factors in relapsed and refractory classical Hodgkin lymphoma undergoing salvage chemotherapy followed by stem cell transplantation. This retrospective study included 101 adult patients being treated at a single center in the period between 1995-2014. The most commonly used salvage chemotherapy was miniBEAM. All patients received BEAM myeloablative protocol followed by stem cell reinfusion. The ORR was 92.1%. After a median of follow-up of 42 months, 5-year OS rate was 56% with 5-year PFS rate being 51%. In each survival curve, a plateau was achieved implying the curative possibility of autologous stem cell transplantation. Adverse prognostic factors associated with worse OS were presence of B symptoms and anemia at relapse and chemoresistance to salvage chemotherapy, defined as inability to achieve 2nd complete remission. However, in survival curve a plateau was reached indicating that 40% of chemorefractory patients can be cured with this approach. Only prognostic factor associated with inferior PFS was chemoresistance to salvage therapy. Outcomes for patients not responding to or relapsing after stem cell transplantation were less advantageous with 31% and 16% 5-years OS rates, stressing the need for better clinical approach in this subpopulation. Based on our results and according to the literature review, we demonstrate that salvage therapy followed by autologous stem cell transplantation represents a treatment of choice in transplant-eligible patients suffering from relapsed or refractory Hodgkin lymphoma.

Key words: classical Hodgkin lymphoma, salvage chemotherapy, stem cell transplantation, overall survival, prognosis

PRIMARNA HIPERTENZIJA U DJECE I ADOLESCENATA

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Primarna hipertenzija je među najčešćim kroničnim bolestima adolescencije, što se povezuje s epidemijom debljine u dječjoj dobi. Čimbenik je rizika za kasniji razvoj kardiovaskularnih bolesti, a subklinička oštećenja ciljnih organa mogu biti prisutna već u djetinjstvu. Na razvoj kardiovaskularnih bolesti debljina utječe i posredstvom metaboličkih promjena u obliku dislipidemije, inzulinske rezistencije, intolerancije glukoze, šećerne bolesti tip 2 te kronične upale. Majčina debljina, dijabetes i hipertenzija tijekom trudnoće imaju ulogu u fetalnom programiranju kardiovaskularnih bolesti. Neinvazivne metode kojima najčešće procjenjujemo funkcionalne i strukturne promjene na krvnim žilama su mjerenje debljine intime-medije karotidnih arterija (cIMT) i mjerenje krutosti arterija. U otkrivanju hipertenzije bijele kute i skrivene hipertenzije ključnu ulogu ima kontinuirano mjerenje arterijskog tlaka (KMAT). Kliničko praćenje te poticanje promjene životnih navika važno je i kod prehipertenzije te hipertenzije bijele kute, budući da i ta stanja nose rizik za oštećenje ciljnih organa. Važna je rana intervencija, jer su promjene u početku reverzibilne, no s vremenom mogu postati fiksirane. Kod izolirane sistoličke hipertenzije centralni aortni tlak je često uredan. S obzirom da o povezanosti izolirane sistoličke hipertenzije s kardiovaskularnim događajima u odrasloj dobi za sada nema dovoljno podataka razumno je redovito praćenje i takvih adolescenata.

Ključne riječi: primarna hipertenzija, hipertenzija bijele kute, skrivena hipertenzija, krutost arterija, djeca i adolescenti

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UVOD

Prevalencija hipertenzije u djece je zadnjih godina u porastu pa u djece od 8 do 18 godina iznosi 2-3,6 %, a u adolescenata od 18 godina oko 10 %. Oduvijek se smatralo da je hipertenzija u dječjoj dobi rijetka i da je u pravilu sekundarna, uzrokovana najčešće bolešću bubrega. Međutim, vidimo da se slika hipertenzije u djece promijenila - primarna hipertenzija danas je jedna od najčešćih kroničnih bolesti u adolescenciji (1). Iako se vjerojatno radi o multifaktorskim uzrocima ove pojave (prekomjeran unos soli, manjak tjelesne aktivnosti, stres), sigurno je da tome značajno pridonosi epidemija debljine u djece koja se dogodila u zadnjem desetljeću. S obzirom na to da je primarna hipertenzija već u dječjoj dobi nerijetko povezana sa subkliničkim oštećenjima ciljnih organa, metaboličkim i imunološkim promjenama u organizmu, ne smatramo je jednostavnim hemodinamskim problemom, već prvim stadijem u razvoju kardiovaskularnih bolesti. Novije spoznaje o fetalnom programiranju buduće hipertenzije i debljine bacaju novo svjetlo na etiologiju i patogenezu kardiovaskularnih bolesti.

DEFINICIJA HIPERTENZIJE U DJECE

Za razliku od odraslih, hipertenzija u djece definirana je na temelju distribucije normalnih vrijednosti arterijskog tlaka u zdravoj populaciji a ne na temelju kardiovaskularnog morbiditeta i mortaliteta vezanog za određenu vrijednost arterijskog tlaka. Hipertenzijom u djece smatramo vrijednosti sistoličkog i/ili dijastoličkog tlaka većim od 95. percentile za dob, spol i tjelesnu visinu izmjerenih u tri odvojena mjerenja. Vrijednosti

<90. percentile smatramo normotenzijom, vrijednosti od 90-95. percentile prehipertenzijom. Hipertenzijom I. stupnja smatramo vrijednosti sistoličkog i/ili dijastoličkog tlaka ≥95. do 99. percentile + 5 mm Hg, a hipertenzijom II. stupnja >99. percentile +5 mm Hg.

Novost u preporukama *European Society of Hypertension* (ESH) iz 2016. godine (2) jest da hipertenziju u adolescenata u dobi ≥16 godina klasificiramo kao u odraslih. Normotenzijom smatramo vrijednosti sistoličkog i/ili dijastoličkog tlaka <130/85 mm Hg, a hipertenzijom vrijednosti ≥130/85 mm Hg. Vrijednosti 130–139/85–90 mm Hg , kao i u odraslih, smatramo prehipertenzijom ili visoko normalnim tlakom , a vrijednosti ≥140/90 mm Hg hipertenzijom.

ARTERIJSKI TLAK I RIZIK ZA OŠTEĆENJE CILJNIH ORGANA

Primarna hipertenzija u djece nije bezazlena i može uzrokovati značajno oštećenje ciljnih organa koje se ponekad registrira već u trenutku postavljanja dijagnoze. Iako su kardiovaskularne bolesti vrlo rijetke u djetinjstvu, oštećenje ciljnih organa je značajan rizik za kardiovaskularne događaje u odrasloj dobi. Povišeni arterijski tlak (AT) može već u dječjoj i adolescentnoj dobi izazvati različite promjene na ciljnim organima - povećanje debljine intime medije karotidnih arterija (engl. cIMT - „*carotid Intima-Media Thickness*"), smanjenu rastezljivost brahijalne arterije, povećanu brzinu širenja pulsnog vala (engl. PWV, *Pulse Wave Velocity*) kroz arterijsku stijenku i augmentacijski indeks (AIx) što ukazuje na povećanu krutost arterija, zatim hipertrofiiju lijeve klijetke (engl. LVH, *Left Vetricular Hypertrophy)*), oštećenje bubrega te promjene na očnoj pozadini (3,4). Novost je da danas imamo normalne vrijednosti za cIMT(5) i za PWV (6) za djecu. Osim toga, u nekoliko longitudinalnih studija utvrđeno je da je povišeni arterijski tlak u djetinjstvu, osobito adolescenciji, povezan s promjenama ciljnih organa u odrasloj dobi – povećanom debljinom intime medije karotidnih arterija (7), povećanom brzinom širenja pulsnoga vala (8) i hipertrofijom lijeve klijetke.

DEBLJINA, HIPERTENZIJA I KARDIOVASKULARNI RIZICI

Zadnjih desetljeća evidentan je porast hipertenzije i debljine u djece i adolescenata te debljina postaje sve veći medicinski problem. Prevalencija prekomjerne tjelesne mase i debljine u djece u različitim zemljama je i do 20-30 %, a prevalencija debljine oko 5-6 %. Povezanost debljine i hipertenzije u djece uočena je u brojnim studijama koje redom ukazuju na povećanu prevalenciju hipertenzije u djece s prekomjernom tjelesnom masom. Osim hipertenzije, uz debljinu su vezani i drugi mogući poremećaji kao dislipidemija, inzulinska rezistencija, intolerancija glukoze, dijabetes melitus tip 2, hipertrofija lijeve klijetke i kronična upala, što sve povećava rizik za kardiovaskularne bolesti u odrasloj dobi. Jedan rizični faktor za razvoj kardiovaskularne bolesti ima 39 % pretile djece, 16,5 % ih ima dva rizična faktora, a 2,8 % tri rizična faktora. Najčešće je to hiperinzulinizam (30,8 %), zatim dislipidemija (12,9 %) i hipertenzija (10,5 %). Dokazana je i korelacija između inzulinske rezistencije i povišenih vrijednosti AT-a u djece (9). Budući da je zadnjih godina masno tkivo označeno kao metabolički i endokrinološki vrlo aktivan organ, važno je utvrditi koja djeca s prekomjernom tjelesnom masom imaju rizik za razvoj hipertenzije i kardiovaskularnih bolesti. Rizik za hipertenziju i druge kardiometaboličke rizične faktore u odrasloj dobi za osobe koje su bile prekomjerno teške i debele u djetinjstvu je povećan (RR 2,7; CI 95 2,2-3,3). Međutim, ako ta djeca izrastu u odrasle osobe normalne tjelesne mase, rizici su jednaki kao u onih koji u djetinjstvu nisu bili pretili (10). Slični su podatci za cIMT u odnosu na povišene vrijednosti AT i količinu visceralnog masnog tkiva u djetinjstvu (11-12). Longitudinalne studije ukazuju na niži rizik za hipertenziju i kardiovaskularne bolesti u osoba koje su bile pretile u adolescenciji i smršavile, a povećani rizik za one trajno prekomjerno teške i pretile od djetinjstva do odrasle dobi (13). Rezultati tih studija podupiru nužnost prevencije i liječenja debljine u djece.

PREHIPERTENZIJA

Prehipertenzija u djece i adolescenata definirana je vrijednostima sistoličkog i/ili dijastoličkog tlaka većim od 90. percentile, ali manjim od 95. percentile za dob spol i tjelesnu visinu. Međutim, 90. percentila sistoličkog i/ili dijastoličkog tlaka u adolescenata je nerijetko viša od 120/80 mm Hg, što je granična vrijednost u odraslih. U tom slučaju prehipertenzijom smatramo vrijednosti arterijskog tlaka (AT) između 120/80 mm Hg (čak i ako su manje od 90. percentile) i 95. percentile za dob, spol i tjelesnu visinu. S obzirom da zadnjih godina i u djece koristimo 24-satno kontinuirano mjerenje arterijskog tlaka (KMAT), prehipertenzija je definirana vrijednostima srednjeg 24-satnog AT-a manjim od 95. percentile uz tlačno opterećenje (engl. *BP load*), odnosno postotak izmjerenih vrijednosti iznad 95. percentile veći od 25. Prevalencija prehipretenzije u dječjoj dobi u različitim studijama iznosi i do 23,7 % (14), ako je AT mjeren samo jednom, odnosno 3,4-4 % ako je mjeren u više navrata. Prehipertenzija je vezana za prekomjernu tjelesnu masu pa tako se nalazi u

13,6 % djece normalnog indeksa tjelesne mase (ITM), u prekomjerno teške djece u 19,7 %, a u debele djece u 23,7 %. (9).

Pitanje je koliko je značenje prehipertenzije u dječjoj dobi? Iako se blago povišenim vrijednostima AT-a u adolescentnoj dobi nerijetko ne obraća osobita pozornost, dva su bitna problema koja povezujemo s prehipertenzijom - rizik progresije u hipertenziju i prisutno oštećenje ciljnih organa. Incidencija hipertenzije u skupini normotenzivne djece je 0,3 % godišnje, dok je u djece s prehipertenzijom 1,1 % godišnje. Povećani rizik za razvoj hipertenzije imaju i adolescenti kod kojih se povremeno mjere blago povišene, ali i normalne vrijednosti AT-a te takvu djecu ipak ne možemo smatrati normotenzivnom. Incidencija hipertenzije u skupini djece koja su rizična za hipertenziju – a to su adolescenti s prehipertenzijom i oni u kojih je početno izmjeren povišeni AT, koji je kasnije bio normalan, je 1,4 % godišnje. Ako su povišene vrijednosti AT-a registrirane u adolescenata u tri mjerenja - stopa razvoja hipertenzije u toj skupini je čak 6,6 % godišnje. To znači da je rizik za razvoj hipertenzije bitno veći u djece i adolescenata s prehipertenzijom, nego u normotenzivne djece (15). Osim rizika za razvoj hipertenzije, u djece s prehipertenzijom nalazimo već i oštećenje ciljnih organa. U više je studija u njih nađena hipertrofija lijeve klijetke, dijastolička disfunkcija, veća debljina intime medije te povećana krutost arterija (16,17) što ima kliničko značenje za razvoj kardiovaskularnih bolesti u odrasloj dobi. Osobito je važna činjenica da su mnoge od tih promjena, prisutnih u adolescenata s prehipertenzijom, reverzibilne, ako se na vrijeme započne promjenom načina života.

HIPERTENZIJA BIJELE KUTE, SKRIVENA HIPERTENZIJA

Hipertenzija bijele kute (engl. WCH, „*white coat hypertension*“) u djece je definirana povišenim vrijednostima arterijskog tlaka mjerenima u liječničkoj ordinaciji većim od 95. percentile, uz normalne vrijednosti izvan ordinacije, odnosno dobivene KMAT-om. Prisutnost WCH obično ukazuje na osobe koje i u drugim stresnim situacijama reagiraju povišenim arterijskim tlakom. Prevalencija u djece jako varira: od vrlo niske (1 %) pa do visoke (45 %), ovisno o kriterijima za postavljanje dijagnoze. Hipertenzija bijele kute češća je u djevojčica, u pretile djece, u djece niske porođajne mase, a primijećeno je i da se češće javlja obiteljski. Prije je smatrana benignom pojavom, no s obzirom da se u te djece mogu naći oštećenja ciljnih organa, u prvom redu LVH, jasno je da WCH ima kliničko značenje i da je rizik za kardiovaskularne bolesti. Važno je pratiti tu djecu kako bi se na vrijeme registrirala stabilna hipertenzija. Iako nema jasnih preporuka za liječenje, medikamentno liječenje se preporučuje, ako postoje znaci oštećenja ciljnih organa (18).

Pojava suprotna hipertenziji bijele kute je tzv. skrivena hipertenzija (engl. MH, „*masked hypertension*“) . Karakterizirana je povišenim vrijednostima AT-a zabilježenim KMAT-om uz normalne vrijednosti mjerene u ordinaciji. Ta djeca često već u ordinaciji imaju vrijednosti AT-a na gornjoj granici normale ili između 90. i 95. percentile. Skrivenu hipertenziju nije lako dijagnosticirati, ali na nju treba misliti ako nam se klinička prezentacija (npr. ehokardiografski nalaz hipertrofije lijeve klijetke) ne poklapa s mjerenim vrijednostima AT-a. Prevalencija skrivene hipertenzije u djece je oko 7 % (19), a u pretilih mladih 19 %. Za precizne podatke o prevalenciji MH u dječjoj populaciji bit će potrebno učiniti KMAT velikom broju zdrave djece. U djece sa skrivenom hipertenzijom, kao i kod djece s hipertenzijom bijele kute, također nalazimo oštećenje ciljnih organa, što ukazuje na njezino kliničko značenje u nastanku kardiovaskularnih bolesti (19). Ta djeca imaju u značajnom postotku veću srčanu frekvenciju, veći ITM nego zdrava djeca, a 50 % ih ima pozitivnu obiteljsku anamnezu za hipertenziju. Iako nije praktično stavljati KMAT zdravoj djeci kako bi se postavila dijagnoza MH, svakako bi ga trebalo učiniti kod djece s visokim rizikom za hipertenziju u odrasloj dobi, osobito djeci s obiteljskom anamnezom hipertenzije. Kontinuirano mjerenje arterijskog tlaka je dobro poznata metoda koja se već dugo primjenjuje u dijagnostici i praćenju hipertenzije u odraslih, ali se tek zadnje vrijeme koristi u djece i adolescenata. Stoga je *American Heart Association* (AHA) donijela preporuke za upotrebu u djece, prvi put 2008. godine, a obnovljene su 2014. godine (4) (tablica 1). KMAT koristimo za razlikovanje prave hipertenzije i hipertenzije bijele kute, za otkrivanje skrivene hipertenzije, u dijagnostici sekundarne hipertenzije, kod djece s kroničnom bubrežnom bolešću, dijabetesom, pretilošću, u nekim genetskim bolestima, pri praćenju učinka antihipertenzivnog liječenja.

Tablica 1.
Izmijenjena shema za interpretaciju kontinuiranog mjerenja arterijskog tlaka (KMAT), 2014.god. (4)

Klasifikacija	AT u ordinaciji	Srednji SBP ili DBP (KMAT)	Sistoličko ili dijastoličko tlačno opterećenje *(load)* (%)
Normalan	<90 c	<95 c	< 25
Hipertenzija bijele kute	≥ 95 c	<95 c	< 25
Prehipertenzija	≥ 90 c ili >120/80	<95 c	≥25
Skrivena hipertenzija	<95 c	> 95 c	≥25
Hipertenzija	> 95 c	> 95 c	25-50
Teška hipertenzija	> 95 c	> 95 c	>50

IZOLIRANA SISTOLIČKA HIPERTENZIJA U ADOLESCENATA I MLADIH

Izoliranu sistoličku hipertenziju (ISH) nalazimo u starih osoba, ali i u adolescenata i mladih, no patofiziološki mehanizam nastanka je potpuno drugačiji. U starih osoba izolirana sistolička hipertenzija znak je povećane krutosti aorte i brzog širenja pulsnog vala anterogradno od srca prema periferiji i retrogradno prema srcu te ranog dolaska retrogradnog vala (u sistoli), koji uzrokuje povećanje sistoličkog tlaka. U mladih ISH nastaje na periferiji zbog tzv. fenomena amplifikacije, tj. pojačanja sistoličkog vala na mjestima grananja velikih arterija prema periferiji uz vrlo elastičnu aortu. Centralni aortni tlak je normalno niži nego brahijalni. Vrijednost centralnog aortnog tlaka dobivamo izračunom iz neinvazivno registriranog pulsnog vala na periferiji (npr. brahijalna ili radijalna arterija). Iako se sve preporuke za hipertenziju osnivaju na brahijalnom tlaku, centralni aortni tlak se smatra vrijednijim parametrom za nastanak budućih kardiovaskularnih događaja, nego brahijalni tlak. Izolirana sistolička hipertenzija u mladih nerijetko se naziva i „lažna hipertenzija", jer se uz povišenu vrijednost sistoličkog tlaka u brahijalnoj arteriji često nalazi normalan centralni aortni tlak. To bi značilo da nalaz povišenog sistoličkog tlaka u takve osobe nema kliničko značenje. Međutim, mišljenja o značenju ISH u mladih su neusklađena i još nema sigurnih odgovora na pitanje u kolikom su riziku za nastanak prave hipertenzije i budućih kardiovaskularnih događaja. U studijama u kojima su praćene mlade osobe sa ISH dobiveni su različiti rezultati. U jednoj studiji je nađen relativno malen rizik za pravu hipertenziju u osoba koje su imale ISH ako je njihov centralni aortni tlak bio nizak (20). U *Anglo-Cardiff Colaborative Trial* studiji na 4700 mladih osoba s ISH nađen je povećani pulsni tlak u odnosu na normotenzivne osobe, ali i povećani udarni volumen, što povećava rizik za nastanak prave hipertenzije i ima kliničko značenje. Međutim, u nekim studijama je u mladih osoba s ISH nađen povišeni centralni aortni tlak i povećana krutost arterija, što ih svrstava u skupinu povećanog rizika za nastanak prave hipertenzije (21,22). Mlade osobe s ISH se ne može svrstati u kategoriju hipertenzivnih, ali budući da ne možemo sa sigurnošću znati kakav će biti ishod u odrasloj dobi i da li će se razviti prava hipertenzija, potrebno ih je pratiti, čak i one s normalnim centralnim aortnim tlakom.

HIPERTENZIJA I VASKULARNI FENOTIP

Povijesno, krvne žile su smatrane pasivnim sustavom za provođenje krvi, ali danas se zna da su one aktivni sudionici u kardiovaskularnoj funkciji. Prva stepenica u određivanju kardiovaskularnog rizika u mladih je mjerenje arterijskog tlaka, ali za potpuniju ocjenu potrebno je odrediti vaskularnu funkciju. Vaskularna funkcija se oštećuje starenjem, ali i zbog različitih bolesti – hipertenzije, debljine, dijabetesa, hiperlipidemije. Hipertenzija može biti uzrok, ali i posljedica oštećene vaskularne funkcije. Povećana krutost arterija je nezavisni rizični faktor za nastanak kardiovaskularnih bolesti. Starenjem i utjecajem raznih štetnih faktora krvne žile postaju krute i ireverzibilno strukturno promijenjene, no u mladih osoba zbog hipertenzije i debljine najprije nastaju reverzibilne, funkcionalne promjene vaskularnog stabla. One vremenom mogu postati fiksirane i ireverzibilne ako hipertenzija traje. Upravo stoga je važna rana intervencija u mladih s hipertenzijom, jer su promjene na ciljnim organima u toj fazi još reverzibilne (23). Više studija ukazuje na povezanost hipertenzije u djece i adolescenata, krutosti arterija i kardiovasularnih rizika (16,24). U svrhu ocjene vaskularne funkcije koristimo nove neinvazivne dijagnostičke metode kojima definiramo status velikih krvnih žila. U odraslih su najčešće upotrebljavani parametri cIMT, PWV i AIX, no oni još uvijek nisu zaživjeli u rutinskoj upotrebi u pedijatrijskoj praksi. Razlog je nedostatak opreme, kompliciranа tehnologija, nedostatna standardizacija metoda, nedostatak iskustva i vještine, nedovoljno definirano značenje u dijagnostici i nedostatak validacije u pedijatijskih pacijenata. Do nedavno nismo imali normalne vrijednosti parametara krutosti arterija za djecu i adolescente, no sada je publicirano nekoliko studija s normalnim vrijednostima za PWV u djece i adolescenata (6,25,26).

INTRAUTERINI ČIMBENICI NASTANKA HIPERTENZIJE

Osnovna pretpostavka „teorije razvojnog podrijetla zdravlja i bolesti" (engl. teorija DOHaD -*Developmental Origin of Health and Disease*) je da na stanje zdravlja i rizik od bolesti u djetinjstvu i u odrasloj dobi direktno utječu čimbenici okoline koji djeluju tijekom prekoncepcijskog, prenatalnog i ranog postnatalnog razdoblja. Začetnici te ideje bili su DJP Barker i CN Hales 80-tih godina prošlog stoljeća, koji su ukazali na obrnutu korelaciju porodne težine i smrtnosti od koronarne bolesti u odrasloj dobi, kao i utjecaj čimbenika iz fetalnog razdoblja na razvoj hipertenzije u odrasloj dobi (27,28). Tijekom svog razvoja fetus je ovisan o majčinoj nutritivnoj, hormonskoj i metaboličkoj ravnoteži, a svaka promjena u programiranju organske strukture, staničnog sastava i genske ekspresije u fetusa može značajno promijeniti njegov metabolizam i funkcije. Adaptaciju na nepovoljne intrauterine uvjete omogućava „razvojna plastičnost" fetusa, a pri tome nastale promjene u tkivima i organima osiguravaju

preživljavanje organizma i ostaju za čitav život. S vremenom je postalo jasno da je mala porođajna težina samo surogat biljeg za procese koji se događaju tijekom intrauterinog života, ako se fetus razvija u nepovoljnim okolnostima. Majčina debljina, neadekvatna prehrana tijekom trudnoće, dijabetes te hipertenzija u trudnoći važni su čimbenici u fetalnom programiranju kroničnih bolesti. Povišene vrijednosti arterijskog tlaka registrirane su u adolescenata čije su majke tijekom trudnoće imale preeklampsiju ili gestacijsku hipertenziju (29). Nekoliko je mogućih mehanizama kojima bi se moglo objasniti perinatalno programiranje kroničnih bolesti, pa tako i hipertenzije, nastalih zbog suboptimalnih uvjeta tijekom fetalnog razdoblja. Moguće je da se radi o smanjenoj veličini različitih organa - dokazano manji broj nefrona u osoba male porođajne mase (30), izmijenjenoj neuroendokrinoj funkciji kao i epigenetskim promjenama. Epigenetika podrazumijeva stabilne, potencijalno nasljedne promjene u funkciji gena i staničnog fenotipa nastale tijekom prenatalnog i ranog postnatalnog razdoblja pod utjecajem čimbenika okoliša, a bez promjene u genskoj sekvenci. Još uvijek nema dovoljno studija koje bi pojasnile utjecaj epigenetskih mehanizama na patofiziologiju kardiovaskularnih bolesti (31).

ZAKLJUČAK:

Primarna hipertenzija je među najčešćim kroničnim bolestima adolescencije što se povezuje s epidemijom debljine u dječjoj dobi. Čimbenik je rizika za kasniji razvoj kardiovaskularnih bolesti, a subklinička oštećenja ciljnih organa, koja su najprije reverzibilna, a zatim postaju fiksirana, prisutna su već u djetinjstvu. Majčina debljina, dijabetes te hipertenzija tijekom trudnoće imaju ulogu u fetalnom programiranju kardiovaskularnih bolesti.U otkrivanju skrivene hipertenzije ključnu ulogu ima kontinuirano mjerenje arterijskog tlaka (KMAT).

Redovito praćenje i poticanje promjene životnih navika važno je i kod prehipertenzije te hipertenzije bijele kute, budući da i ta stanja nose rizik oštećenja ciljnih organa, a za sada je razumno i kod adolescenata s izoliranom sistoličkom hipertenzijom.

L I T E R A T U R A

1. Litwin M, Michalkiewicz J,Gackowska L. Primary hypertension in children and adolescents is an immuno-metabolic disease with hemodynamic consequences. Curr Hypertens Rep 2013; 15: 331-9.

2. Lurbe E, Agabiti-Rosei E, Cruickshank JK i sur. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens 2016; 34: 1887-920.

3. Falkner B. Recent clinical and translational advances in pediatric hypertension. Hypertension 2015; 65: 926-31.

4. Flynn JT, Daniels SR, Hayman LL i sur. Update: ambulatory blood pressure monitoring in children and adolescents: a scientific statement from the American Heart Association. Hypertension 2014; 63: 1116-35.

5.Doyon A, Kracht D, Bayazit AK i sur. Carotid artery intima-media thickness and distensibility in children and adolescents: reference values and role of body dimensions. Hypertension 2013; 62: 550-6.

6. Hidvegi EV, Illyes M, Benczur B i sur. Reference values of aortic pulse wave velocity in a large healthy population aged between 3 and 18 years. J Hypertens 2012; 30: 2314-21.

7. Juonala M, Magnussen CG, Venn A i sur. Influence of age on associations between childhood risk factors and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study for the International Childhood Cardiovascular Cohort (i3C) Consortium. Circulation 2010; 122: 2514-20.

8. Koivistoinen T, Hutri-Kahonen N, Juonala M. Metabolic syndrome in childhood and increased arterial stiffness in adulthood: the Cardiovascular Risk In Young Finns Study. Ann Med 2011; 43: 312-9.

9. Lurbe E, Ingelfinger JR. Blood pressure in children and adolescents: current insights. J Hypertens 2015;

10. Juonala M, Magnussen CG, Berenson GS i sur. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N Engl J Med 2011; 365: 1876-85.

11. Juhola J, Magnussen CG, Berenson GS i sur. Combined effects of child and adult elevated blood pressure on subclinical atherosclerosis: the International Childhood Cardiovascular Cohort Consortium. Circulation 2013; 128: 217-24.

12. Ferreira I, van de Laar RJ, Prins MH, Twisk JW, Stehouwer CD. Carotid stiffness in young adults: a life-course analysis of its early determinants: the Amsterdam Growth and Health Longitudinal Study. Hypertension 2012; 59: 54-61.

13. Suglia SF, Clark CJ, Gary-Webb TL. Adolescent obesity, change in weight status, and hypertension: racial/ethnic variations. Hypertension 2013; 61: 290-5.

14. Haas GM, Bertsch T, Schwandt P. Prehypertension and cardiovascular risk factors in children and adolescents participating in the community-based prevention education program family heart study. Int J Prev Med 2014; 5: S50-6.

15. Redwine KM, Daniels SR. Prehypertension in adolescents: risk and progression. J Clin Hypertens (Greenwich). 2012; 14: 360-4.

16. Urbina EM, Khoury PR, McCoy C, Daniels SR, Kimball TR, Dolan LM. Cardiac and vascular consequences of pre-hypertension in youth. J Clin Hypertens (Greenwich) 2011; 13: 332-42.

17. Drukteinis JS, Roman MJ, Fabsitz RR i sur. Cardiac and systemic hemodynamic characteristics of hypertension and prehypertension in adolescents and young adults: the Strong Heart Study. Circulation 2007; 115: 221-7.

18. Jurko A Jr., Minarik M, Jurko T, Tonhajzerova I. White coat hypertension in pediatrics. Ital J Pediatr 2016; 42: 4.

19. Lurbe E, Torro I, Alvarez V i sur. Prevalence, persistence, and clinical significance of masked hypertension in youth. Hypertension 2005; 45: 493-8.

20. Saladini F, Santonastaso M, Mos L i sur. Isolated systolic hypertension of young-to-middle-age individuals implies a relatively low risk of developing hypertension needing treatment when central blood pressure is low. J Hypertens 2011; 29: 1311-9.

21. O'Rourke MF, Adji A. Guidelines on guidelines: focus on isolated systolic hypertension in youth. J Hypertens 2013; 31: 649-54.

22. O'Rourke MF, Adji A. Isolated systolic hypertension in the young: a need for clarity. Reply. J Hypertens 2013; 31: 1913-4.

23. Litwin M, Niemirska A, Sladowska-Kozlowska J i sur. Regression of target organ damage in children and adolescents with primary hypertension. Pediatr Nephrol 2010; 25: 2489-99.

24. Stabouli S, Papakatsika S, Kotronis G, Papadopoulou-Legbelou K, Rizos Z, Kotsis V. Arterial stiffness and SBP variability in children and adolescents. J Hypertens 2015; 33: 88-95.

25. Reusz GS, Cseprekal O, Temmar M i sur. Reference values of pulse wave velocity in healthy children and teenagers. Hypertension 2010; 56: 217-24.

26. Elmenhorst J, Hulpke-Wette M, Barta C, Dalla Pozza R, Springer S, Oberhoffer R. Percentiles for central blood pressure and pulse wave velocity in children and adolescents recorded with an oscillometric device. Atherosclerosis 2015; 238: 9-16.

27. Barker DJ. The fetal origins of adult hypertension. J Hypertens Suppl. 1992; 10: S39-44.

28. Barker DJ. Fetal origins of coronary heart disease. BMJ 1995; 311: 171-4.

29. Fraser A, Nelson SM, Macdonald-Wallis C, Sattar N, Lawlor DA. Hypertensive disorders of pregnancy and cardiometabolic health in adolescent offspring. Hypertension 2013; 62: 614-20.

30. Hughson M, Farris AB 3rd, Douglas-Denton R, Hoy WE, Bertram JF. Glomerular number and size in autopsy kidneys: the relationship to birth weight. Kidney Int. 2003; 63: 2113-22.

31. Breton CV, Park C, Siegmund K i sur. NOS1 methylation and carotid artery intima-media thickness in children. Circ Cardiovasc Genet. 2014;7:116-22.

SUMMARY

PRIMARY HYPERTENSION IN CHILDREN AND ADOLESCENTS

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Primary hypertension is among the most common chronic diseases in adolescence, which is associated with the epidemic of childhood obesity. It presents a risk factor for later development of cardiovascular diseases, and subclinical damages to target organs can occur as early as childhood. Obesity influences development of cardiovascular diseases through metabolic changes such as dyslipidemia, insulin resistance, glucose intolerance, diabetes mellitus type 2, and chronic inflammation. Maternal obesity, diabetes and hypertension during pregnancy play a role in fetal programming of cardiovascular diseases. Noninvasive methods most often used to estimate functional and structural changes in blood vessels measure the carotid intima-media thickness (cIMT) and arterial stiffness. Ambulatory blood pressure monitoring (ABPM) plays a key role in detecting white coat hypertension and masked hypertension. Clinical monitoring and encouraging lifestyle modifications are important considering both prehypertension and white coat hypertension, as these conditions also pose a risk in target organ damage. Early intervention is important because these changes are reversible in the beginning, but can become stable with time. In isolated systolic hypertension, central aortic pressure is often within normal values. Since not enough information has yet been gathered on the connection between isolated systolic hypertension and cardiovascular events in adulthood, it is prudent to regularly monitor such adolescents.

Key words: primary hypertension, white coat hypertension, masked hypertension, arterial stiffness, children and adolescents

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FIZIČKA AKTIVNOST I ŠEĆERNA BOLEST

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Sve veća učestalost šećerne bolesti povezuje se s prihvaćanjem netradicionalnih načina prehrane i prakticiranjem „sjedilačkog načina života". Liječenje šećerne bolesti sastoji se od promjene životnog stila što uključuje promjenu fizičke aktivnosti, tipa i učestalosti prehrane te uzimanje specifične terapije. Fizička aktivnost je dio temeljnog liječenja dijabetesa; ima dokazane koristi u smanjenju inzulinske rezistencije, poboljšanju glikemijske kontrole, lipidnog profila, u normalizaciji tjelesne mase i povećanju kardiorespiracijske sposobnosti. Vježbanje može smanjiti potrebu za lijekovima i usporiti razvoj nekih dijabetičkih komplikacija. U osoba koje se liječe od šećerne bolesti postoje i određena ograničenja, što se uglavnom odnosi na one s prisutnim komplikacijama. Prije započinjanja programa fizičke aktivnosti preporučuje se učiniti medicinsku evaluaciju te dati adekvatne upute. Tjelovježba se prakticira uz spoznaju da za vrijeme i poslije intenzivnih vježbi glukoza u plazmi pada zbog njene povećane potrošnje, ali i povećane inzulinske osjetljivosti. Bolesnici koji su liječeni inzulinom ili inzulinskim sekretagozima imaju veći rizik od hipoglikemije pa se količina unesenih kalorija prilagođava tipu i intenzitetu fzičke aktivnosti, daju se jasne upute glede prilagodbe terapije prije i/ili nakon tjelovježbe. Šećerna bolest nije prepreka za bavljenje sportom, no zahtijeva angažiranost i znanje, kako medicinskog tima koji prati bolesnika, tako i bolesnika s šećernom bolešću samog.

Ključne riječi: šećerna bolest, tjelovježba, sport

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FIZIČKA AKTIVNOST I ŠEĆERNA BOLEST

Šećerna bolest je kronična bolest koja nastaje kada gušterača ne proizvodi dovoljno inzulina, ili kada tijelo ne može učinkovito iskoristiti proizvedeni inzulin. Šećerna bolest se ne promatra kao izolirani poremećaj glikemije nego kao „... heterogena grupa metaboličkih poremećaja karakterizirana trajnom hiperglikemijom, .dok je kronična hiperglikemija vezana uz poremećaj metabolizma ugljikohidrata, masti i proteina, nastala kao poremećaj sekrecije inzulina, njegovog djelovanja ili oboje."(1).

Svjetska zdravstvena organizacija procjenjuje da je broj osoba sa šećernom bolesti porastao sa 108 milijuna u 1980. godini na 422 milijuna u 2014. godini (1). Očekuje se najveći porast šećerne bolesti u zemljama koje su sada u razvoju, vjerojatno kao posljedica prihvaćanja specifičnih netradicionalnih načina prehrane i mijenjanja životnih navika. Epidemiju šećerne veže se uz epidemiju debljine. Kako se debljina javlja u sve mlađoj životnoj dobi, za očekivati je da će i udio osoba koje su niz godina pretile biti sve veći i da će se one prakticirajući „sjedilački način života" sve manje kretati. Populacija stari i metaboličke posljedice bit će izraženije pa se može očekivati da će incidencija dijabetesa biti sve veća. S druge strane, na veći ukupan broj oboljelih od dijabetesa utječe i činjenica da se o dijabetičkim osobama sve bolje skrbi i da imaju dulji životni vijek.

Dva najčešća tipa šećerne bolesti su tip 1 i tip 2. U tipu 1 dijabetesa dolazi do autoimunoga razaranja β-stanica u Langerhansovim otočićima gušterače koje izlučuju inzulin. Kao posljedica destrukcije stanica nema više sinteze inzulina te dolazi do njegovog apsolutnog manjka. Ranije je nazvan inzulin-ovisni, jer je životno

potrebno liječenje inzulinom Radi od 5 % do 10 % slučajeva svih dijabetesa. On je najčešći je u djece i mlađih osoba te se nekada nazivao i juvenilnim dijabetesom. Čak i do trećine slučajeva novonađenog tipa 1 javlja se u dobi iznad 30 godina pa se naziv juvenilni izbjegava. (2). Većinu dijagnosticiranih dijabetesa čini onaj tipa 2. Kod tipa 2 niz različitih, nasljednih i okolišnih čimbenika utječe na njegovu pojavu, manifestaciju i brzinu razvoja. Etiologija nije do kraja poznata, nego elementi „mozaika" koji ga čine. Postavka u kojoj nasljedni faktor (možda poligenski) nosi rizik, a trigerira ga okolišni (npr. debljina) je prihvaćeni model (3,4). Četiri elementa koja metabolički determiniraju dijabetes tipa 2 su debljina, inzulinska rezistencija, disfunkcija sekrecije inzulina i pojačana sinteza endogene glukoze. Oko 90 % svih dijagnosticiranih dijabetesa čini tip 2.

Sama narav šećerne bolesti nije jednostavna, kao ni njena etiologija, pa se ne može simplificirati niti pitanje terapije. Kako postoji više tipova dijabetesa, postoji i više modaliteta terapije koji nisu primjenjivi za svaki tip. Svaka osoba sa svojim kliničkim stanjem, navikama i psihofizičkim mogućnostima te motiviranošću dijelom diktira tip liječenja. Cilj liječenja dijabetesa nije isključivo dobra kontrola glikemije, nego i uplitanje u patofiziologiju same bolesti i čuvanje rezervi endogenog inzulina što dulje (što se odnosi na tip 2). Cilj terapije također nije samo izbjegavanje akutnih komplikacija, nego mogućnost da osoba sa šećernom bolesti živi što dulje i kvalitetnije s minimumom kroničnih komplikacija (5,6). Kronične komplikacije dijabetesa sa svojim mutilirajućim završnim stupnjevima sve više zauzimaju vodeća mjesta u neurološkim, oftalmološkim i nefrološkim odjelima, a osobe s generaliziranom aterosklerozom te srčanim i cerebrovaskularnim komplikacijama često boluju od dijabetesa. Liječenje šećerne bolesti zahtijeva maksimalni angažman samog bolesnika jer uključuje mijenjanje čitavog životnog stila, od promjene fizičke aktivnosti, tipa i učestalosti prehrane pa tek onda uzimanje specifične terapije. Liječenje se sastoji od edukacije, adekvatne fizičke aktivnosti, prehrambenih modifikacija. U tipu 2 šećerne bolesti liječenje uključuje niz oralnih antidijabetika, inzulina, te neinzulinske supkutane terapije. U tipu 1 dijabetesa je neminovan inzulin, takav se bolesnik može liječiti uz više dnevnih injekcija inzulina i inzulinskom crpkom te transplantacijom gušterače.

TJELOVJEŽBA KAO TERAPIJA ŠEĆERNE BOLESTI

Početak liječenja dijabetesa jest saznanje da dijabetes postoji. Saznanje za tip 1 dijabetesa najčešće započinje akutnom fazom bolesti, a saznanje za tip 2 kasni oko 5-6 godina od početka bolesti. Epidemiološki podatci o porastu debljine i uz nju dijabetesa tipa 2 zapravo ukazuju na potrebu prvog stupnja edukacije koji je na razini javnozdravstvenih akcija kao npr. ukazivanje na potrebu mijenjanja životnih navika i unaprjeđenje zdravlja općenito (..krećete li se i vi 30 minuta dnevno). Tako se osvješćuje mogućnost pojave dijabetesa i u osoba koje ga trenutno nemaju, ali su obiteljski opterećene ili nose faktore rizika. Još su antički narodi preporučili tjelovježbu, odnosno tjelesnu aktivnost, kao bitan dio svakodnevnog života.

Nakon postavljanja dijagnoze započinje se tzv. temeljnim liječenjem - uputama o potrebi promjene stila života što uključuje savjetovanje o prehrani i fizičkoj aktivnosti. Fizička aktivnost je temeljni i bitan sastojak ukupnoga programa liječenja šećerne bolesti te sprječavanja kardiovaskularnih komplikacija. Ona pokazuje višestruke koristi kao što su npr. povećanje kardiorespiracijske sposobnosti, povećanje snage, smanjenje inzulinske rezistencije, poboljšanje glikemijske kontrole, unaprjeđenje lipidnog profila, održavanje tjelesne mase (7,8). Meta-analize su pokazale da nadzirani režimi koji uključuju vježbe snage i aerobne vježbe poboljšavaju glikemijsku kontrolu u odraslih bolesnika sa šećernom bolešću tipa 2 (9). Klinički je dokazano da su umjerena do visoka razina fizičke aktivnosti i kardiorespiracijska sposobnost udružene sa smanjenjem morbiditeta i mortaliteta bolesnika i s tipom 1 i s tipom 2 šećerne bolesti (10,11).

Vježbanje može smanjiti potrebu za lijekovima, a i usporiti razvoj nekih dijabetičkih komplikacija. Međutim, u osoba koje se liječe od šećerne bolesti postoje i određena ograničenja što se uglavnom odnosi na one s postojećim komplikacijama. Radi navedenog, prije samog započinjanja programa fizičke aktivnosti jačeg intenziteta i snage od šetnje, bolesnici s dijabetesom trebaju biti medicinski evaluirani uzimajući u obzir stanja koja bi mogla biti kontraindikacija za određeni tip vježbi. Neke od njih bi mogle dovesti do ozljede ili povećati rizik za srčanožilni događaj.

Aerobne vježbe ne dovode do duga kisika pa se preporučuje minimum aerobne tjelesne aktivnosti od 150 minuta tjedno umjerenog intenziteta, raspoređeno u najmanje tri navrata, s razmakom od maksimalno dva dana između pojedinih treninga. Kako anaerobne vježbe dovode do duga kisika, preporučuje se intervalno vježbanje koje se kombinira s razdobljima odmora ili aerobne tjelesne aktivnosti. Bolesnici sa šećernom bolešću koji započinju vježbe snage trebali bi imati inicijalne instrukcije, povremene savjete i praćenje trenera. Tjelovježba se prakticira uz spoznaju da za vrijeme i poslije intenzivnih vježbi glukoza u plazmi pada zbog njene povećane potrošnje, ali i povećane inzulinske osjetljivosti. Izrazito je bitno imati na umu da se količina unesenih kalorija mora modificirati prema tipu aktivnosti koja se provodi i tjelesnoj težini.

ŠEĆERNA BOLESTI TIPA 2 I TJELOVJEŽBA

Poznato je da i osobe koje imaju intoleranciju glukoze mogu redovitom tjelovježbom smanjiti razvoj šećerne bolesti (12). One osobe koje već imaju tip 2 šećerne bolesti i trajno vježbaju mogu ne samo regulirati aktualnu glikemiju nego i utjecati na trajnu glukoregulaciju uz smanjenje vjerojatnosti kroničnih komplikacija (13). Tjelovježba utječe na smanjenje inzulinske rezistencije, smanjenje hiperinzulinemije čime se zadire u samu srž tipa 2 dijabetesa. Inzulinska rezistencija se smanjuje povećanom ekspresijom perifernih GLUT 4 receptora, a ako se želi postići korist koja bi smanjila i lipidemiju potrebna je rigoroznija i napornija vježba (14). Tijekom tjelovježbe otpušta se dušični oksid te dolazi do blage vazodilatacije čime se može regulirati i hipertenzija. U šećernoj bolesti tipa 2 s redovitom fizičkom aktivnošću i/ili srednjom do visokom kardiorespiracijskom sposobnošću, dokazano je smanjen srčanožilini i ukupni mortalitet 39-70 % tijekom 15-20 godina praćenja (15). Postoje određeni rizici tjelovježbe - one osobe koje uzimanju inzulin u terapiji ili se liječe inzulinskim sekretagozima kao npr. sulfnilurejama imaju veći rizik od hipoglikemije. Potrebno je navesti da postoji mogućnost hipoglikemije i u duljem razdoblju nakon tjelovježbe zbog povećane inzulinske osjetljivosti (16). Za sportaše koji imaju tip 2 šećerne bolesti, i one koji se rekreativno bave sportom danas postoji cijeli spektar lijekova koji ne dovodi do hipoglikemije (metformin, lijekovi temeljeni na inkretinskom učinku, inhibitori natrij-glukoza kotransportera 2, pioglitazon) (17). Takvom terapijom se omogućuje bolesnicima s tipom 2 dijabetesa da se bave fizičkom aktivnošću bez straha od hipoglikemije ili bez potrebe uzimanja dodatnih obroka. One osobe koje uzimaju premiješani inzulin (kombinacija srednjedugodjelujućeg i kratko/ultrakratkodjelujućeg inzulina) mogu vježbati prije uzimanja inzulina uz redukciju doze ili uz izbacivanje kratkodjelujuće komponente inzulina, tj. ako ga uzimaju u dvije doze ujutro i navečer vježbati oko podneva kada obrok nije terapijski pokriven kratkodjelujućim inzulinom. Oni bolesnici s tipom 2 dijabetesa koji se liječe po shemi bazal/bolus (više dnevnih injekcija uz bazalni srednjedugodjelujući ili dugodjelujući inzulin i boluse prandijalnog inzulina) podešavaju dozu bolusa aktualnoj glikemiji i intenzitetu tjelovježbe. Kako većina bolesnika s tipom 2 dijabetesa ima povećan srčanožilni rizik, potrebno je imati na umu da neadekvatno opterećenje može precipitirati ishemiju miokarda. Prije početka primjene tjelovježbe potrebno je, prema procjeni liječnika, učiniti EKG, a kod bolesnika s povišenim kardiovaskularnim rizikom učiniti ergometriju. Bolesnicima s razvijenom teškom retinopatijom uz intenzivniju tjelesnu aktivnost može doći do njenog pogoršanja, tj. može izazvati krvarenje iz oštećenih krvnih žila u retini (bolesnici s retinopatijom trebali bi se poštedjeti izrazitih napora ili npr. manevara sličnih Valsalvi) (18). Kod onih koji imaju neuropatiju postoji veći rizik od ozljeda, čak neprimjetnih malih na stopalima koje mogu u svom kasnijem tijeku dovesti do upale. Neadekvatna obuća može otvoriti ulkus te dovesti do infekcije što se kasnije dugotrajno i teško liječi, infekcije ili deformacija. Autonomna neuropatija ponekad ograničava normalnu adaptaciju srčane frekvencije te čini limitirajući faktor za vježbanje. Preporučuje se da bolesnik s dijabetesom uz sve navedene ograde vježba aerobno umjerenim intenzitetom 30 minuta ili dulje, no vježba ne bi trebala povećati puls na više od 60-70 % bazalnog. Tjelovježba bi trebala početi zagrijavanjem koje traje oko 5-10 minuta, rastezanjem tj. „strechingom", nakon toga maksimalno 30 minuta treninga uz monitoriranje srčane frekvencije do željenih vrijednosti i najmanje 10 minuta postupnom obustavom vježbi tzv. „hlađenjem". Kako često vježbati pitanje je na koje je odgovor - što češće, najbolje svaki dan, no ipak ne manje od 3 x tjedno. Praktično najlakše izvediva aerobna vježba u većine sredovječnih i starijih bolesnika sa šećernom bolešću je hodanje koje se može lako prilagoditi te imati elemente i aerobne i anaerobne vježbe. Umjereno brzo hodanje na ravnom je kao oblik aerobne vježbe, žustro hodanje uzbrdo i trčanje kao oblik intenzivne aerobne vježbe. Najveći utjecaj vježbi snage na regulaciju glikemije imaju bolesnici koji vježbaju 3 seta vježbi visokog intenziteta (8 puta po setu) 3 puta na tjedan (19,20).

ŠEĆERNA BOLESTI TIPA 1 I TJELOVJEŽBA

Šećerna bolest tipa 1 je kronična bolest koja ponajprije pogađa mlađu populaciju te uključuje kompleksne mjere liječenja edukacijom, dijetom, inzulinom i tjelesnom aktivnošću. Radi neminovne primjene inzulina potrebno je prilagoditi njegovu dozu i vrijeme aplikacije tjelovježbi, tj. prilagoditi unos ugljikohidrata. Radi se o mladim ljudima koji teže fizičkoj aktivnosti kao i njihovi vršnjaci, često su nerealno limitirani samom bolešću što je izraženo tijekom djetinjstva i adolescencije. U istraživanju bolesnika sa šećernom bolesti tipa 1 obrađivanih u sklopu dnevne bolnice Zavoda za endokrinologiju KBC-a Zagreb procijenjena je razina tjelesne aktivnosti Međunarodnim upitnikom tjelesne aktivnosti (engl. *International Physical Activity Questionnaire* – IPAQ) te se došlo do rezultata da značajna proporcija ispitanika sa šećernom bolesti tipa 1 (87,5 %) spada u skupinu visoko i umjereno tjelesno aktivnih osoba (21). Stoga ne čudi da postoji velik broj mladih ljudi s tipom 1 šećerne bolesti koji se svakodnevno bave ciljanom fizičkom aktivnosti, a neki od njih i profesionalnim sportom. Postoji i profesionalni biciklistički tim, u kojem svi sportaši oboljeli od dijabetesa tipa 1 ostvaruju vrhunske sportske rezultate (22). Niz profesionalnih sportaša boluje od tipa 1 dijabetesa, a jedan od njih je i

nositelj olimpijskog zlata (23). Takvi rezultati pokazuju da dijabetes nije prepreka za bavljenje sportom, no zahtijeva veliku angažiranost i znanje, kako medicinskog tima koji prati bolesnika, tako i samog bolesnika.

Mišić je organ koji može primiti glukozu i bez inzulina što je izraženije za vrijeme tjelovježbe pa se glikemija tada spontano smanjuje osobito za vrijeme aerobnih aktivnosti. Za vrijeme mirovanja 10 % energije u mišiću dolazi od glikogenolize, do 90 % oksidacije masnih kiselina a samo pokoji postotak od aminokiselina. Uz početak tjelovježbe počinju se naglo trošiti zalihe glikogena uz sintezu laktata - nakon nekoliko minuta dolazi do vazodilatacije, povećanog protoka kroz mišiće i utilizacije glukoze iz krvi. Također se aktivira lipoliza te se pojačano otpuštaju slobodne masne kiseline i glicerol. Koliko će se trošiti glukoza, a koliko masne kiseline ovisi o naravi tjelovježbe, njenom intenzitetu i trajanju. Što je tjelovježba dulja, to su ugljikohidrati značajniji kao energenti. Dolazi do pada razine inzulina i rasta glukagona. Osobe koje imaju o inzulinu ovisan tip dijabetesa mogu smanjivati glikemiju te ev. ući u stanje hipoglikemije. Postoji i tzv. hipoglikemija koja se javlja nakon tjelovježbe, nekoliko sati do jednog dana nakon vježbanja, a smatra se da nastaje kao posljedica smanjene inzulinske rezistencije. U slučajevima kada se tijekom tjelovježbe ili druge fizičke aktivnosti ekscesivno luče kateholamini može doći i do paradoksne hiperglikemije pa sve do dijabetičke ketoacidoze (23). Tipičan porast glikemije je oko 15 min nakon vježbanja; nastaje kada zbog supresije inzulina i lučenja kontraregulatornih hormona dolazi do pojačane glukoneogeneze. Pojava ketoze do ketoacidoze nastaje kada se vježba izvodi uz deficit inzulina te dolazi do naglog porasta glikemije. Tjelovježba metabolički ide u prilog lipolizi pri čemu se stvaraju ketonska tijela. Kao rizik tjelovježbe u tipu 1 (kao i u tipu 2) uz poremećaj regulacije glikemije navode se ozljede, pojačana proteinurija, mogućnost ablacije retine i vitrealnog krvarenja, a u bolesnika sa ishemičkom bolesti srca povećan je rizik od akutnog koronarnog incidenta. Iz navedenih se razloga preporučuje bolesnicima s tipom 1 šećerne bolesti koji imaju više od 35 godina, ili šećernu bolest dulje od 15 godina uz poznate komplikacije prije vježbanja učiniti test opterećenja (24). Unatoč svemu navedenom, inzulinska terapija nije prepreka tjelovježbi što dokazuju poznati sportaši koji se liječe inzulinom (25). Kada i kako vježbati određuje osobna preferencija, realne mogućnosti i tip inzulinske terapije (više dnevnih injekcija ili inzulinska crpka). Vježba bi trebala biti planirana, ako je moguće 1 do 3 sata nakon obroka. Obvezno je mjerenje razine glukoze u krvi prije tjelovježbe; ono se izbjegava ako je GUP manja od okvirno 4,4 mmol/L ili veća od oko 13,6 mmol/L uz prisutnu ketonuriju, tj. ako je GUP veći od 16,6 mmol/L bez ketonurije. Kod nižih vrijednosti glikemije trebala bi se smanjiti doza inzulina prije početka tjelovježbe i osigurati obrok u slučaju pojave hipoglikemije (26). Uputno je češće mjeriti glikemiju tijekom dugotrajnije tjelovježbe te aplicirati inzulin dalje od mjesta mišićnih skupina koje će se najviše koristiti. Ako se radi o dugotrajnijem fizičkom naporu može se dodati obrok (za vrijeme vježbanja i /ili nakon njega), tj. specijalizirani nutritivni pripravci prilagođeni dijabetičarima. Kod vježbi koje se ponavljaju s velikim intenzitetom, a kratkog su trajanja dodaje se malo inzulina. Osobe koje se liječe frakcioniranim dozama mogu lako reducirati dozu prije vježbe i do pola predviđene doze, a nakon vježbe iduću dozu prilagoditi postojećoj glikemiji. Osnova tjelovježbe u tipu 1 je planirana tjelovježba: znači da bi trebala postojati ideja kako se dugo vježba i kojim intenzitetom, koliko nakon i prije uzimanja inzulina, mora postojati dodatna hrana i mogućnost mjerenja glikemije. Kada se planira dugotrajna tjelovježba (duža od oko 4 sata) potrebno je reducirati dozu kratkodjelujućeg prandijalnog inzulina za 30-50 %, smanjiti dozu kratkodjelujućeg inzulina pred idući obrok te imajući na umu dugotrajni učinak tjelovježbe reducirati i iduću dozu dugodjelujućeg inzulina (27). Kod planiranja vježbe nakon jela može se reducirati doza kratkodjelujućeg inzulina ovisno o aktualnoj glikemiji i planiranom intenzitetu vježbi te planirati tjelovježbu u doba oko 2 sata nakon obroka. Jutarnja tjelovježba donosi i manji rizik od hipoglikemije (veća je inzulinska rezistencija).

Inzulinska pumpa je medicinsko pomagalo koje omogućuje kontinuirano supkutano snabdijevanje organizma inzulinom u promjenjivim, prilagodljivim i preciznim dozama tijekom 24 sata. Namijenjena je liječenju dijabetičara tipa 1. Kontinuirana isporuka pokriva bazalnu sekreciju inzulina kao zamjenu za fiziološko bazalno lučenje inzulina (bazalni ritam) što je kod osoba oboljelih od šećerne bolesti koji se liječe s više injekcija inzulina/dan, zamjena za inzulin srednjedugog, tj. dugog djelovanja. Osobe koje su liječene inzulinskom pumpom mogu prilagođavati vrijednost bazalnog inzulina tjelovježbi (u potpunosti isključiti inzulinsku pumpu, smanjiti na određeno aktivniji, nakon vježbanja zbog kasnog učinka tjelesne aktivnosti umjereno reducirati bazalnu vrijednosti na npr. 70 % itd.) (28). Inzulinska pumpa također omogućuje bolesniku da prema vlastitoj prosudbi dodaje inzulin uz obrok (bolus doza), a navedeno zamjenjuje fiziološki porast inzulina nakon jela i situaciju kada bolesnik koji se liječi s više injekcija inzulina prije obroka aplicira inzulin kratkog ili ultrakratkog djelovanja. Dozu inzulina uvjetuje količina ugljikohidrata u obroku koji slijedi, uz dodatak eventualne korekcije hiperglikemije. Koliko je do sada poznato, inzulinska pumpa je najvjerniji način imitacije prirodne inzulinske sekrecije te je, izuzev transplantacije gušterače, najveći terapijski doseg u liječenju šećerne bolesti. Mnogi mladi ljudi koji boluju od tipa 1 dijabetesa i aktivno se bave fizičkom aktivnošću nose inzulinsku pumpu.

L I T E R A T U R A

1. Bennet PH, Knowler WC. Definition, diagnosis and clasification of diabetes mellitus and Glucose homeostasis U: Kahn CR, Weir GC, King GL, Jacobson AM, Moses AC, Smith RJ. Joslin's Diabetes mellitus 14 th edition. Boston: Joslin'diaetes center: 2016

2. Global report on diabetes. World Health Organization, Geneva, 2016 Dostupno na URL adresi: http://www.who.int/mediacentre/factsheets/fs312/en/ Datum pristupa informaciji 15 studenog 2016

3. Laakso M, Pyorala K. Age at onset and type of diabetes. Diabetes Care 1985; 8: 114 7.

4. Halter JB, Graf RJ, Porte D Jr. Potentiation of insulin secretory responses by plasma glucose levels in man: evidence that hyperglycemia in diabetes compensates for impaired glucose potentiation. J Clin Endocrinol Metab 1979; 48: 946-54.

5. Yoneda H, Ikagami H, Yamamoto Y i sur. Analysis of early phase insulin responses in non-obese subjects with mild glucose intolerance. Diabetes Care 1992; 15: 1517-21.

6. Diabetes Control and Complications Trial (DCCT) Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 30: 977-86.

7. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 12: 854-65.

8. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C, White RD. Physical activity/exercise and type 2 diabetes: a consensus statement from the American Diabetes Association. Diabetes Care 2006; 29:1433-8.

9. Wing RR, Goldstein MG, Acton KJ i sur. Behavioral science research in diabetes: lifestyle changes related to obesity, eating behavior, and physical activity. Diabetes Care 2001; 24: 117-23.

10. Snowling NJ, Hopkins WG. Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. Diabetes Care. 2006; 29: 2518-27.

11. Gregg EW, Gerzoff RB, Caspersen CJ, Williamson DF, Narayan KM. Relationship of walking to mortality among US adults with diabetes. Arch Intern Med 2003; 163: 1440-7.

12. Hu G, Jousilahti P, Barengo NC i sur. Physical activity, cardiovascular risk factors, and mortality among Finnish adults with diabetes. Diabetes Care 2005; 28: 799-805.

13. Tataranni PA, Bogardus C. Changing habits to delay diabetes. N Engl J Med 2001; 344: 1390-2.

14. Schneider SH, Amorosa LF, Khachadurian AK, Ruderman NB. Studies on the mechanism of improved glucose control during regular exercise in type 2(non-insulin-dependent) diabetes. Diabetologia 1984; 26: 355-60.

15. Dos Santos JM, Moreli ML, Tewari S, Benite-Ribeiro SA. The effect of exercise on skeletal muscle glucose uptake in type 2 diabetes: An epigenetic perspective. Metabolism 2015; 64: 1619-28.

16. Church TS, LaMonte MJ, Barlow CE, Blair SN. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. Arch Intern Med 2005; 165: 2114-20.

17. Cusi K, Maezono K, Osman A i sur. Insulin resistance differentially affects the PI3-kinase- and MAP kinase-mediated signaling in human muscle. J Clin Invest 2000; 105: 311-20.

18. Baretić M, Troskot R. How to fight obesity with antidiabetic drugs: targeting gut or kidney? Minerva Endocrinol 2015; 40: 71-83.

19. American College of Sports Medicine. Guidelines for exercise testing and prescription, 5th ed. Philadelphia: Lea & Febiger, 1995.

20. Castaneda C, Layne JE, Munoz-Orians L i sur. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. Diabetes Care 2002; 25: 2335-41.

21. Dunstan DW, Daly RM, Owen N i sur. High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. Diabetes Care 2002; 25: 1729-36.

22. Kovač D, Babić-Naglić K, Pavlić-Renar I i sur. Tjelesna aktivnost bolesnika sa šećernom bolesti tip 1. Reumatizam 2013; 60: 125.

23. Racing with diabetes Dostupno na URL adresi: http://www.teamnovonordisk.com/_Datum pristupa informaciji 15 studenog 2016

24. Type 1 diabetes. Dostupno na URL adresi: http://www.typ1diabetes.com/gary_hall_olympic_swimmer_diabetes.htm Datum pristupa informaciji 15 studenog 2016

25. Berger M, Berchtold P, Cüppers HJ i sur. Metabolic and hormonal effects of muscular exercise in juvenile type diabetics. Diabetologia 1977; 13: 355-65.

26. LaPorte RE, Dorman JS, Tajima N i sur. Pittsburgh Insulin-Dependent Diabetes Mellitus Morbidity and Mortality Study: physical activity and diabetic complications. Pediatrics 1986; 78: 1027-33.

27. Coleman SK, Rebalka IA, D'Souza DM, Hawke TJ. Skeletal muscle as a therapeutic target for delaying type 1 diabetic complications. World J Diabetes 201; 6: 1323-36.

28. Diabetes mellitus and exercise. American Diabetes Association. Diabetes Care 1997; 20: 1908-12.

29. Toni S, Reali MF, Barni F, Lenzi L, Festini F. Managing insulin therapy during exercise in type 1 diabetes mellitus. Acta Biomed 2006;77: 34-40.

30. Baretić M, Kraljević I, Renar IP. Nocturnal Hypoglycemia-The Main Indication For Insulin Pump Therapy In Adulthood. Acta Clin Croat 2016; 55: 93-9.

SUMMARY

PHYSICAL ACTIVITY AND DIABETES MELLITUS

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The increasing incidence of diabetes is associated with constant lifestyle changes including non-traditional dietary patterns and lack of physical activity, i.e. sedentary lifestyle. Basic treatment of diabetes involves healthy eating (modification of type and frequency of meals), regular exercise and, in some cases, diabetes medication or insulin therapy. Physical activity is always part of the basic treatment of diabetes. It is also important as a specific aspect of health promotion and disease prevention. There are many proven benefits of exercise in diabetes, e.g., reduction of insulin resistance, improvement of glycemic control and lipid profile. Exercise also reduces body weight and increases cardiorespiratory capacity. The benefits of physical activity improve most of the metabolic abnormalities in type 2 diabetes. Exercise can even reduce the demand for drugs and slow development of some diabetic complications. One of the easiest and most appropriate types of physical activity is walking. It is recommended that individuals perform moderate physical activity for 30 minutes daily, i.e. moderate-to-vigorous intensity aerobic exercise at least 5 days a week, or a total of 150 minutes per week. Even small increases in physical activity show benefit. Prior to starting an exercise program, diabetic patients should be screened for the presence of macro- and microvascular complications. Some chronic complications may worsen with exercise and these patients have some limitations regarding duration and type of physical activity. There is specific activity limitation in diabetic retinopathy, ischemic heart disease and for diabetic patients with loss of protective sensation. Patients should be instructed to wear proper footwear and examine their feet daily for lesions. During and after intense exercise, plasma glucose falls due to the increased glucose utilization and increased insulin sensitivity. Hypoglycemia can occur during, immediately after, or hours after exercise. With proper instructions, hypoglycemia can be avoided. Patients treated with insulin or insulin secretagogues have a risk of hypoglycemia. Such patients should be instructed to modify the amount of calories according to the type of activity and body weight. It is necessary to give instructions about customization of therapy before and/or after exercise. For people with type 1 diabetes willing to exercise (especially those planning professional sports or extreme exercise), it is important to balance insulin doses with food and activity. Blood glucose must be self-monitored and response to physical activity evaluated; if blood glucose is initially too low or too high, exercise must be delayed. For such patents, insulin pump therapy is a good solution; a number of professional athletes are treated with insulin pumps. The majority of people with diabetes can exercise safely as long as certain precautions are taken. Patients with diabetes should be able to enjoy sports and many benefits of physical activities. Finally, diabetes is not an obstacle to participation in sports, although it requires commitment and knowledge of both the medical team and the patient. When choosing the type of physical activity, personal preference must be also taken in consideration.

Key words: diabetes, physical activity, sports

DIAGNOSING MACROAMYLASEMIA IN UNEXPLAINED HYPERAMYLASEMIA

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Macroamylasemia is a curious condition marked by hyperamylasemia without any other signs or symptoms, most frequently caused by immunoglobulin-amylase complexes that cannot be secreted normally by the kidneys. It usually requires no additional investigation, but must be taken into consideration to avoid unnecessary diagnostics and treatment, which burden both the patient and the healthcare system. A number of studies and reports have described macroamylasemia in combination with other conditions or diseases, one of the more interesting being celiac disease, where a gluten free diet was shown to cure both. Our case presents a young female patient without significant signs or symptoms except for elevated serum amylase discovered by chance, and ignored. Macroamylasemia was considered and confirmed, while celiac disease was subsequently excluded.

Key words: hyperamylasemia, laboratory diagnosis, macroamylasemia

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INTRODUCTION

Macroamylasemia, a rare but otherwise benign condition, is characterized by hyperamylasemia or elevated serum amylase levels without elevated urine amylase and other signs or symptoms (1-6). In macroamylasemia, amylase is bound by immunoglobulin, making it larger than usual and unable to be filtered by the kidneys, resulting in high serum amylase levels but normal urine levels (1-6). Various papers report different statistics on the incidence of macroamylasemia, it is clear that it is more common among adults, although cases in infants and children have been reported. As hyperamylasemia is the cornerstone for diagnosing pancreatitis, a much more serious condition that requires additional work-up and in most cases hospitalization, it is important for physicians at the primary or secondary level to be able to recognize and diagnose macroamylasemia in order to avoid further diagnostic and treatment measures, or to avoid changing current treatment when considering comorbidity (1-4,7). Further testing puts unnecessary strain on various areas of the healthcare system taking time for work with other patients, not to mention the stress on patients, especially when further investigation or treatment is generally not required (1-4,7).

An accepted algorithm for confirming a diagnosis of macroamylasemia, after first finding elevated serum amylase without elevated urine amylase, is to subsequently test for serum lipase, which together with high amylase levels usually suggests pancreatitis (1-4,6,8). If serum lipase is normal, kidney function must be tested, as abnormal renal function would also cause elevated levels (1-4,6). Once normal kidney function is confirmed, renal amylase clearance relative to cre-

atinine clearance should be calculated (see Appendix); normal ratios are between 3% and 5%, where a result of less than 1% suggests macroamylasemia (1-4,6,8). The final confirming test is electrophoresis or polyethylene glycol precipitation test and chromatography (1,2,8,10). Unfortunately, these methods are not routinely used, at least not in Croatia, and laboratories are not offering or performing such tests, but most authors would agree that the ratio calculation can be considered diagnostic, although there is disagreement about the issue (2,4-9,11).

CASE REPORT

A 27-year-old female patient visited doctor's office for the first time. The patient had no complaints other than known fatigue due to sideropenic anemia from menstrual bleeding, which the patient regularly followed-up with laboratory tests (blood count, iron, UIBC, TIBC and ferritin levels), and was taking iron as needed. The patient described gastroesophageal reflux disease (occasional nausea, heartburn and abdominal pain), and was aware of elevated serum amylase without elevated urine amylase after routine check-up with laboratory tests a couple of years before. No further investigation was undertaken, but the patient regularly underwent laboratory testing for serum and urine amylase, and the results were always the same. Her appetite, urine and stool were normal. Menstrual cycles were normal, some cycles were abundant, but her last gynecologic examination was normal. The patient did not smoke or drink. Allergies were denied and the patient did not take any regular medication. The patient denied other serious conditions or diseases except for scoliosis that was followed-up, treated with an orthosis and physical therapy, and operated due to severity. She also denied any other significant medical history except for multiple hospitalizations (more than five) as a child due to abdominal pain, nausea and vomiting that had led to severe dehydration, but no further explanation or diagnosis had ever been found. Family history was unremarkable.

Examination of her previous medical documentation confirmed the patient's interview, including multiple hospitalizations for vomiting and severe dehydration. Several tests were performed during this time (laboratory tests, upper gastrointestinal series, abdominal ultrasound) and all proved normal, with the exception of hiatal hernia, and metabolic acidosis and acetonuria. Test results for serum and urine amylase were also found and both were within the reference values: serum amylase 90 U/L (ref. <90) and urine amylase 339 U/L (ref. <390).

Physical examination was unremarkable. Fresh laboratory test results, just as the patient described, showed elevated serum amylase 143 U/L (ref. 23-91) but normal urine amylase 57 U/L (ref. <400). Follow up laboratory test for serum lipase was normal, 44 U/L (ref. 13-60). Renal function was normal and renal amylase clearance relative to creatinine clearance was calculated (see Appendix) and found to be 0.8% (ref. 3%-5%). Although the aforementioned hospitalizations were initially misleading, the interview, physical examination and test results suggested the diagnosis of macroamylasemia to be very likely; only electrophoresis was lacking.

Laboratory tests for celiac disease were negative: serum IgA 1.3 g/L (ref. 0.7-4.0) and anti-tissue transglutaminase-IgA (anti-tTG-IgA) <2 RU/mL (ref. negative <20, positive >20).

DISCUSSION

Amylase is an enzyme that is responsible for the breakdown of amylase and other starches during digestion. It exists as three subtypes, where α-amylase is found in animals, including humans, and it is the only one of clinical importance (6).

Although hyperamylasemia is associated with pancreatitis in particular, there are other conditions and diseases that may present with hyperamylasemia as well, all of which would require further investigations, unlike macroamylasemia, including sialadenitis, pulmonary disease, ovarian cysts, ruptured ectopic pregnancy, abdominal trauma, mesenteric infarction, perforated peptic ulcer, appendicitis, pelvic inflammatory disease, renal failure, mumps and carcinoma (1,2,6,8,12). Things can get tricky when macroamylasemia is found in cases that would normally present with hyperamylasemia, as in a case of appendicitis presenting with hyperamylasemia as caused by macroamylasemia (6). Another interesting case found macroamylasemia in a patient with elevated serum amylase levels, elevated urine levels and a raised clearance ratio, not characteristic of macroamylasemia. After various tests, it was concluded that elevated serum amylase levels were due to macroamylasemia, while urine values were due to salivary amylase being produced by renal cell carcinoma (12). Naturally, these patients exhibited other signs and symptoms which suggested comorbidity (6,12). Some studies report an increased incidence of macroamylasemia in HIV positive patients, but at least one study refutes this fact (13). Macroamylasemia has been reported in a case of splenosis after post-traumatic splenectomy (14). Macroamylasemia was even found while following a case of pancreatitis itself (15).

Although macroamylasemia is generally asymptomatic, a number of cases were detected due to abdominal pain, which led to serum and urine amylase measurement, but this does not confirm a relationship between the two (2,6,10). Some authors suggest it is merely a coincidence, since amylase is tested more often when abdominal pain is present (2,10). According to one hypothesis, abdominal pain and macroamylasemia are often found together due to precipitation of macroamylase molecules within the pancreas, although it has not yet been proven (2,6).

Finding hyperamylasemia with other autoimmune conditions or diseases is not uncommon either, and could indicate macroamylasemia instead of pancreatitis or hyperamylasemia associated conditions; examples are systemic lupus erythematosus, rheumatoid arthritis, and ulcerative colitis (2,5,7,16). There also is a case reported in combination with Crohn's disease (7). Many cases of macroamylasemia have been reported together with celiac disease, and one case has even been reported with both celiac disease and myasthenia gravis (5,17-19). A gluten free diet, gluten being the trigger causing celiac disease, has been shown to treat macroamylasemia in these cases (17-19). There are cases of macroamylasemia reported in selective IgA deficiency (20).

There are theories on how macroamylase is formed; one is the antigen driven theory where a self antigen cross reacts with an antibody for a foreign antigen, and the other theory is dysregulation of immune tolerance that occurs in autoimmune diseases (2,5,16,20). In this way, antibodies are formed, in most cases immunoglobulin A, rarely immunoglobulin G, which react to either salivary or pancreatic amylase, or a combination of the two, forming immune complexes, more commonly salivary amylase (2,4,7,9,15). Cases of macroamylasemia and macrolipasemia have also been described, which especially create confusion as elevated amylase and lipase are found in pancreatitis (15,21). Other molecules including α-1 antitrypsin, polysaccharides and glycoproteins have been shown to form complexes with amylase causing macroamylasemia as well (2,7,9,22).

It has also been suggested that polyclonal gammopathy or polyclonal increase of immunoglobulins, often present in autoimmune and lymphoproliferative diseases, may also increase the likelihood of developing macroamylasemia (2,15). Indeed, the condition has been associated with lymphoma, multiple myeloma and myeloid leukemia (5,7,14,15). Although most authors agree that macroamylasemia is a benign condition, diagnosed easily enough, which does not require further investigation or treatment, due to the correlation between polyclonal gammopathy and macroamylasemia it has been suggested that macroamylasemia without any clear cause deserves investigation to rule out autoimmune or lymphoproliferative disease (2,15).

Macroamylasemia may also be induced, as shown by one study where a group of test subjects were infused with a hydroxyethyl starch (HES) solution, which is a volemic colloid used in the management of hypovolemia. The test subjects were all healthy individuals who developed hyperamylasemia after infusion with a HES solution. Hyperamylasemia was proven to be of a macroamylase character. As the HES molecules broke down, hyperamylasemia or macroamylasemia resolved itself. This study proved macroamylasemia to have a potential to be induced iatrogenically as well, apart from disease (2,22).

Some papers report that actually there are three types of macroamylasemia, i.e. classic type (type 1), where serum amylase is elevated, and urine is normal; type 2, where both are elevated; and type 3, where both are normal, but these types have not been studied additionally (2,11).

In cases of serum amylase activity over 100 U/L, macroamylasemia can be confirmed by electrophoresis (1,3). A negative result shows two clearly defined bands (S and P type amylase), while the presence of a 'smeared' band, caused by an immunoglobulin-amylase complex, confirms macroamylasemia (8,10,21,23).

It should be noted that other cases of asymptomatic hyperamylasemia have been described including chronic non-pathological hyperamylasemia of pancreatic origin, ethnic hyperamylasemia, and familial hyperamylasemia (24).

Macroamylasemia fitted our case perfectly, as there were no other symptoms or signs other than elevated serum amylase to suggest pancreatitis or one of the other aforementioned conditions or diseases. Additional simple and inexpensive laboratory tests and calculations (lipase, renal function, renal amylase clearance relative to creatinine clearance) confirmed the diagnosis despite the lack of a confirming test such as electrophoresis, as all evidence clearly pointed to macroamylasemia. However, upon seeing elevated serum amylase, a physician who does not take macroamylasemia into consideration would be forced to investigate, ordering unnecessary tests and examinations. It is unclear why hyperamylasemia was originally ignored in our case, but definitive benign diagnosis was certainly welcome. Celiac disease was considered due to the connection found in the aforementioned cases and studies between macroamylasemia and celiac disease, and the presentation of atypical features of celiac disease in our patient (nonspecific gastrointestinal complaints, iron deficiency anemia and short stature), but was excluded with additional laboratory tests for serum IgA and anti-tTG-IgA.

APPENDIX

Renal amylase clearance relative to creatinine clearance:
Serum creatinine 60 μmol/L (ref. 49-90)
Urine creatinine 2.9 mmol/L (no reference for random sample)
Serum amylase 143 U/L (ref. 23-91)
Urine amylase 57 U/L (fef. <400)

Formula = urine amylase / serum amylase x serum creatinine / urine creatinine x 100
= 57 U/L / 143 U/L x 60 μmol/L / 2900 μmol/L x 100
= 0.40 x 0.02 x 100
= 0.80%

REFERENCES

1. LeVine D, Parrish D. Macroamylasemia: a simple stepwise approach to diagnosis. J Gen JABFP 1989; 2: 279-82.

2. Klonoff DC. Macroamylasemia and other immunoglobulin-complexed enzyme disorders. West J Med 1980; 133: 392-407.

3. Mark LK, McCord RG. Pancreatic scanning in diagnosis of macroamylasemia: case report. J Nucl Med 1977; 18: 130-132.

4. Agarwal J, Deepika G. Macroamylasemia: a benign cause for high serum amylase. Indian Pediatr 2015; 52: 533.

5. Sakallıoğlu O. Macroamylasemia; a dilemma in morbidity. Balkan Med J 2015; 32:330.

6. Um JW, Kim KH, Kang MS *et al.* Macroamylasemia in a patient with acute appendicitis: a case report. J Korean Med Sci 1999; 14: 679-681.

7. Venkataraman D, Howarth L, Beattie RM, Afzal NA. A very high amylase can be benign in paediatric Crohn's disease. BMJ Case Rep 2012; doi: 10.1136/bcr.02.2012.5917

8. Leclerc P, Forest JC. Variations in amylase isoenzymes and lipase during acute pancreatitis, and in other disorders causing hyperamylasemia. Clin Chem 1983; 29: 1020-1023.

9. Gallucci F, Madrid E, Esposito P, Uomo G. Association of macroamylasemia and type I macro-creatine kinasemia: a case report. J Pancreas 2007; 8: 605-608.

10. Leclerc P, Forest JC. Electrophoretic determination of isoamylases in serum with commercially available reagents. Clin Chem 1982; 28: 37-40.

11. Berk JE. Macroamylasemia: a biochemical aberration in search of a disease. West J Med 1980; 133: 433-435.

12. Kazmierczak SC, Van Lente F, McHugh AM, Katzin WE. Macroamylasemia with a markedly increased amylase clearance ratio in a patient with renal cell carcinoma. Clin Chem 1988; 34: 435-438.

13. Szoke D, Ridolfo A, Valente C, Galli M, Panteghini M. Frequency of pancreatic hyperamylasemia in human immunodeficiency virus-positive patients in the highly active antiretroviral therapy era. Am J Clin Pathol 2016; 145: 128-133.

14. Gubergrits NB, Zubov A, Golubova O, Fomenko P, Byelyayeva N. Clinical observation of macroamylasemia in splenosis due to the posttraumatic splenectomy. J Pancreas 2014; 15: 394-398.

15. Cho SY, Lee A, Lee HJ, Suh JT. Overlapping presence of macroamylasemia and hyperamylasemia in acute pancreatitis. Korean J Lab Med 2011; 31: 98-100.

16. Goto H, Wakui H, Komatsuda A, Imai H, Miura AB, Fujita K. Simultaneous macroamylasemia and macrolipasemia in a patient with systemic lupus erythematosus in remission. Intern Med 2000; 39: 1115-1118.

17. Depsames R, Fireman Z, Niv E, Kopelman Y. Macroamylasemia as the first manifestation of celiac disease. Case Rep Gastroenterol 2008; 2: 196-198.

18. De Almeida-Menezes M, Ribeiro-Cabral VL, Lorena SS, Nucci A, Andrade-Santana P, Queiroz Silva C. Rare association of celiac disease with myasthenia gravis in a patient with other immune disorders: a case report. Rev Esp Enferm Dig 2016; 108: 586-588.

19. Barera G, Bazzigaluppi E, Viscardi M *et al.* Macroamylasemia attributable to gluten-related amylase autoantibodies: a case report. Pediatrics 2001; 107: 93.

20. Türkçapar N, Ozyüncü N, Idilman R, Ensari A, Soylu K, Ozden A. Macro-amylasemia in a patient with selective IgA deficiency and antiphospholipid antibodies. Turk J Gastroenterol 2006; 17: 140-143.

21. Zaman Z, Van Orshoven A, Mariën G, Fevery J, Blanckaert N. Simultaneous macroamylasemia and macrolipasemia. Clin Chem 1994; 40:939-942.

22. Mishler JM, Dürr GH. Macroamylasemia induced by hydroxyethyl starch - confirmation by gel filtration analysis of serum and urine. Am J Clin Pathol 1980; 74(4): 387-391.

23. Cobbaert C. Discrepancies between methods for amylase in cases of macroamylasemia. Clin Chem 1991; 37(12): 2159-2160.

24. Koda YK, Vidolin E. Familial hyperamylasemia. Rev Hosp Clin Fac Med Sao Paulo 2002; 57(2): 77-82.

S A Ž E T A K

DIJAGNOSTICIRANJE MAKROAMILAZEMIJE KOD NERAZJAŠNJENE HIPERAMILAZEMIJE

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Makroamilazemija je zanimljivo stanje obilježeno hiperamilazemijom bez ikakvih drugih znakova ili simptoma, najčešće uzrokovana kompleksima imunoglobulina i amilaze koji se ne mogu izlučiti putem bubrega. Najčešće ne zahtijeva proširenu kliničku obradu, ali se mora uzeti u obzir kako bi se izbjegla nepotrebna dijagnostika i liječenje koji mogu predstavljati opterećenje za bolesnika i zdravstveni sustav. Nekoliko studija i prikaza opisuju makroamilazemiju zajedno s drugim stanjima ili bolestima, a jedna od značajnijih je celijakija gdje je primjena bezglutenske dijete osnova liječenja. Naš slučaj predstavlja mladu bolesnicu bez značajnih znakova ili simptoma osim povišene serumske amilaze otkrivene slučajnim probirom. Makroamilazemija je potvrđena bez znakova celijakije, a liječenje nije bilo potrebno.

Ključne riječi: **hiperamilazemija, laboratorijska dijagnostika, makroamilazemija**

KOMUNIKACIJA LIJEČNIKA S MIGRANTIMA I IZBJEGLICAMA

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Važnost komunikacije između pacijenta i liječnika temelj je uspješnog liječenja i upravo je zato sastavni dio preddiplomskog studija medicine, kao i poslijediplomskog osposobljavanja. Mogućnost komunikacije iznimno je važna u međukulturnim odnosima. Liječnici prigodom prevladavanja jezičnih barijera kod migranata i izbjeglica moraju uzeti u obzir i pacijentova sociokulturna uvjerenja, jezične barijere i moguću prisutnost latentnih infekcija te kroničnih bolesti. Kao i pri liječničkom pregledu predstavnika većinske populacije, komunikaciju treba individualno prilagoditi i u slučaju liječenja predstavnika migranata odnosno izbjeglica. Pritom treba uzeti u obzir da ni neverbalna komunikacija nije univerzalna. Liječnici i zdravstveni djelatnici prigodom premošćivanja jezičnih barijera najčešće se služe laičkim tumačima koji u načelu olakšavaju komunikaciju, ali istraživanja su pokazala da mogu imati i negativnu ulogu. Rjeđe se koriste internetskim prevoditeljskim alatima, priručnicima i rječnicima. Bez obzira na pacijentovu kulturnu pozadinu i jezične barijere, liječnik i njegovi suradnici od početka moraju graditi odnos povjerenja zasnovan na međusobnom poštovanju. Liječnici kod pružanja zdravstvene skrbi migrantima moraju uzeti u obzir i specifične stresne čimbenike koji su povezani s migracijom i utječu na pojavnost duševnih smetnji, kao i kad migranti i izbjeglice dulje borave u državi domaćinu.

U članku su najprije predstavljeni opći zaključci u vezi s izbjegličkom problematikom u Europi s naglaskom na komunikaciju. Opisana je problematika tumača i kulturnih posrednika. Autorice na kraju posebno upozoravaju na podcijenjeno vrednovanje mentalnog zdravlja izbjeglica.

Ključne riječi: liječnik, zdravstveni djelatnik, izbjeglica, migrant, komunikacija, zdravstvena skrb

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UVOD

Od početka krize u Siriji broj izbjeglica u Europi neprestano se povećava (1). Migracijskim kretanjima nisu pridonijeli samo izbjeglice iz Sirije nego i migranti koji migriraju zbog ratova ili s gospodarski manje razvijenih područja. Godine 2015. i Slovenija se morala suočiti s izbjegličkom problematikom, jer je kao dio balkanske rute bila važna tzv. tranzitna država za migrante. To za nju nije značilo samo političko-socijalni izazov nego i javnozdravstveni problem (2, 3).

Kriza ljudske mobilnosti s kojom se suočava Europska unija (EU) je kompleksna. Naime, vlade se suočavaju s različitim izazovima pri rješavanju zdravstvenih potreba većeg broja migranata koji dolaze iz različitih dijelova svijeta. U Europi još uvijek ne postoji dorečen standardizirani pristup procjeni zdravstvenih potreba migranata i izbjeglica od kojih su mnogi tijekom više tjedana i mjeseci prošli različite oblike transporta i imali različite mogućnosti pristupa hrani, vodi i smještaju. Zbog mnogobrojnih čimbenika bili su izloženiji riziku od ozljeda i obolijevanja, a uz to su imali različite mogućnosti pristupa zdravstvenim uslugama.

U nekim su državama EU-a početne trijažne procjene i zdravstveni pregledi novopridošlih migranata, ekonomskih migranata i izbjeglica obvezni, a u drugima nisu. Osim toga, sadržaj tih procjena nije usklađen u svim državama EU-a, tako da u okviru zdravstvenih pregleda većina ne dodjeljuje tzv. otpusno pismo ili nalaz. Zato zdravstveno osoblje neke države kod prvog kontakta s novim izbjeglicom ili migrantom ne može procijeniti ni uzeti u obzir podatke prethodnih zdravstvenih pregleda.

PROBLEMATIKA IZBJEGLICA I MIGRANATA

Zdravstvena skrb za migrante i izbjeglice obuhvaća specifične aspekte o kojima se liječnik i drugi zdravstveni djelatnici trebaju raspitati radi osiguravanja kvalitetne zdravstvene skrbi. Bitni su podatci o zemlji podrijetla, uvjetima u izbjegličkim kampovima i centrima za prihvat azilanata, kulturnim i jezičnim barijerama, mogućim latentnim infekcijskim zarazama (tuberkuloza, hepatitis B), kroničnim bolestima, lijekovima, mogućim ozljedama i mučenju te s tim povezanim posttraumatskim stresnim sindromom, depresijom i anksioznošću (4,5).

Zdravstvena problematika izbjeglica i migranata može se podijeliti u više područja:

- pristup zdravstvenoj skrbi
- sredstva za skrb za migrante i s njom povezani troškovi
- komunikacija s pacijentima
- raznolikost bolesti koje se javljaju u toj populaciji
- mogućnost daljnje bolničke zdravstvene skrbi
- psihološka potpora.

U državama koje se već više godina suočavaju s izbjegličkom problematikom različita su istraživanja (6-9) pokazala da je za dobru zdravstvenu skrb ključan individualni pristup. Naime, izbjeglice i ostali migranti dolaze iz različitih okruženja (i urbanih i ruralnih), razlikuju se odgojem, navikama i razinom obrazovanja. Kao i u radu s „lokalnim" pacijentima, i kod skrbi za imigrante i migrante komunikaciju treba prilagoditi svakom pojedincu.

Budući da su Hrvatska i Slovenija bile ponajprije tranzitne države, kod skrbi za izbjeglice bilo je ključno da zdravstveni djelatnici budu dostupni u svim smještajnim centrima, tako da su migranti i izbjeglice znali kome se obratiti u vezi sa svojim zdravstvenim problemima. Potpuno je drugačije kod izbjeglica koji žele ostati u državi i zatražiti azil jer ih treba upoznati s radom zdravstvenog sustava (gdje i kako urediti zdravstveno osiguranje, kome se obratiti u hitnom slučaju, a kome u slučaju ostalih akutnih ili kroničnih problema, gdje se nalaze ambulante liječnika obiteljske medicine, koje je njihovo radno vrijeme itd.).

S medicinskog aspekta, za zdravstvenog je djelatnika važno naučiti o bolestima koje se kod nas pojavljuju rjeđe, a češće su u ostalim dijelovima svijeta. Da bi migrantima i izbjeglicama osim stručne pomoći bilo moguće pružiti i odgovarajuću psihološku potporu, vrlo je važna i suradnja različitih službi (psihijatri, psiholozi, socijalni radnici i dr.) i cjelovit pristup u obradi bolesnika. Za njih je i sam put bio vrlo naporan i stresan, a većina ih je u prošlosti u matičnoj državi doživjela mnogobrojne strahote rata, zlostavljanja i traume. Toga moramo biti svjesni i aktivno ih poticati na traženje pomoći, jer neki i zbog etničkih i/ili vjerskih razloga nisu navikli javno govoriti o takvim događajima. Posebnu pomoć treba pružiti djeci i omogućiti im uključivanje u obrazovni sustav.

Ne smijemo se iznenaditi ako migranti i imigranti očekuju način zdravstvene skrbi na koji su navikli i kakav su dobivali kod kuće. Također, njihova percepcija i interpretacija bolesti mogu biti umnogome drugačije od naših. Neki zbog toga na liječnike stvaraju veći pritisak jer od liječenja možda imaju drukčija očekivanja.

POSEBNOSTI KOMUNIKACIJE S MIGRANTIMA I IZBJEGLICAMA

Izbjeglice i migranti koji su došli balkanskom rutom nisu jedna homogena skupina i nije ih moguće podijeliti na više manjih homogenih skupina, npr. Sirijce, Afganistance, Somalijce itd. Istraživanje sa šengenskog područja (Hrvatska, Slovenija) potvrdilo je rezultate dosad provedenih istraživanja zdravstvene skrbi za migrante, tj. da je najveći problem loša komunikacija. Zbog nje su zdravstveni djelatnici (bili) pod znatno većim stresom zbog moguće pogrešno postavljene dijagnoze i/ili pogrešno određenog liječenja jer je – kao u svim ostalim zdravstvenim disciplinama – i kod skrbi za migrante dobra anamneza ključna za što bolju pruženu skrb.

Kao i u radu s „lokalnim" pacijentima, i kod skrbi za izbjeglice i migrante komunikaciju treba prilagoditi svakom pojedincu. Tu se u komunikaciji javlja i dodatni problem – jezik. Iako prisutnost tumača i kulturnih posrednika u načelu umnogome olakšava komunikaciju, istraživanja su pokazala da oni mogu imati i negativnu ulogu (10). Najprije treba osigurati da budu odgovarajućeg spola (npr. žene tumači kod pregleda migrantica; isto vrijedi i za zdravstvene djelatnike). Kad su tumači odnosno prevoditelji u rodu s bolesnikom, može doći do pogrešne interpretacije; rodbini se neki simptom može činiti više ili manje važan nego onome tko prikuplja anamnezu, zato ga zbog emocionalnog angažmana predstavlja drukčije. Osim toga, u slučaju prisutnosti službenog tumača prilikom pregleda kod osobe se može pojaviti osjećaj srama i nelagode, što ponovno pridonosi netočnosti pruženih informacija koje za zdravstveno osoblje mogu biti od ključne važnosti.

Kod rada s pojedincima iz drugog kulturnog okruženja dobro je poznavati „kulturno uvjetovane sindrome" koji definiraju interakciju i komunikaciju između pacijenta i zdravstvenog osoblja. Neki predstavnici etničkih manjina na zdravstvene probleme reagiraju

vrlo emocionalno. Zbog nerazumijevanja njihova načina izražavanja, zdravstveni djelatnik može ih neodgovarajuće etiketirati kao neurotične. Neki pacijenti, koji pripadaju ekonomskim migrantima, u strahu za radno mjesto minimaliziraju svoje probleme, a liječnika nenamjerno usmjeravaju na drugi dijagnostički algoritam (11). Ni neverbalna komunikacija nije jednostavna. Tako, na primjer, ni kontakt očima nije univerzalan: neki čak neprekidan kontakt očima smatraju napadačkim (12,13).

MOGUĆA RJEŠENJA ZA POBOLJŠANJE KOMUNIKACIJE

Istraživanje John-Baptista i suradnika pokazalo je da je kvaliteta zdravstvene skrbi niža kod bolesnika koji govore strani jezik i nemaju pristup odgovarajućem tumaču ili međukulturnom posredniku koji bi prevodio na njima razumljiv jezik (14). S druge strane, pri uvođenju tumača i međukulturnih posrednika u zdravstvene ustanove ključno je da su stručno osposobljeni za rad u kliničkom okruženju. U nekim državama, kao što su Sjedinjene Američke Države i Australija, prevoditelji odnosno tumači u zdravstvenim se ustanovama obrazuju na nacionalnoj razini (15). S obzirom na to da u slovenskom zdravstvenom sustavu još nemamo profesionalnih tumača i međukulturnih posrednika koji bi bili stručno osposobljeni za rad u zdravstvenim ustanovama, razumljiv je podatak iz još neobjavljenog istraživanja u sklopu kojega je 66 % anketiranih zdravstvenih djelatnika pomoć nestručnih tumača ocijenilo kao učinkovitu. Osim tumačima, anketiranim zdravstvenim djelatnicima često pomažu migrantovi prijatelji odnosno rođaci koji razumiju jezik zdravstvenog osoblja odnosno jezik koji razumiju oba sugovornika. Ali, inozemna istraživanja pokazuju da oslanjanje na nekvalitetno tumačenje koje obavljaju bolesnikovi rođaci i znanci može dovesti do neodgovarajućih i manjkavih dijagnoza, pogrešnog liječenja i prečestih posjeta liječniku te duljih razdoblja ležanja. Lindholm i drugi su zaključili da postoji izravna veza između angažiranja tumača i trajanja hospitalizacije. Na osnovi podataka o 3071 bolesniku obrađenom između 2004. i 2007. godine u tercijarnoj američkoj bolnici koja djeluje u okviru sveučilišta Harvard utvrđeno je da je samo 39 % bolesnika prilikom prijma i otpusta dobilo potporu u obliku tumačenja. Bolesnici koji nisu imali tu potporu bili su hospitalizirani od 0,75 do 1,47 dana dulje i češće su bili ponovo primljeni u bolnicu u roku od 30 dana (16).

U suvremenom svijetu liječnici i njihovi suradnici imaju na raspolaganju i pomagala kao što su internetski prevoditelji i višejezični rječnici. *United Nations High Commissioner for Refugees* nudi tečaj za samostalno učenje namijenjen stručnjacima i početnicima. U projektu *Take Care* navedeni su osnovni izrazi za hitne zdravstvene slučajeve (17). Ti izrazi pomažu liječnicima i zdravstvenom osoblju u sporazumijevanju s migrantima i izbjeglicama u hitnim zdravstvenim slučajevima. Riječ je o popisu najčešće postavljanih pitanja u hitnim zdravstvenim situacijama. Taj je popis na raspolaganju na 17 jezika: engleskom, arapskom, bugarskom, kineskom, hrvatskom, nizozemskom, francuskom, njemačkom, grčkom, litavskom, poljskom, portugalskom, rumunjskom, ruskom, španjolskom, turskom i ukrajinskom. Internetska usluga *Google Translate* i komunikacija uz pomoć ruku, koje su tijekom našeg šengenskog istraživanja morali primjenjivati mnogobrojni zdravstveni djelatnici, mogu značiti dodatnu pomoć, ali ne bi smjele biti glavni oblik komunikacije jer se time gube ili mogu izgubiti mnoge informacije.

Suradnja prevoditelja, kulturnih posrednika i tumača razlikuje se od slučaja do slučaja. U službenim postupcima (npr. podnošenje zahtjeva za međunarodnu zaštitu) uvijek treba biti prisutan prevoditelj. Za te postupke i prevođenje zaduženo je Ministarstvo unutarnjih poslova.

PODCIJENJENA PROBLEMATIKA MENTALNOG ZDRAVLJA KOD IZBJEGLICA

Nakon što su bili izloženi ratnim strahotama i stresnim događajima izbjeglice su u većoj opasnosti da se kod njih razviju problemi s mentalnim zdravljem. Raširenost mentalnih poremećaja iznimno se mijenja (od 75 % do manje od 5 % raširenosti posttraumatskog stresnog poremećaja kod izbjeglica). Sustavni pregledi rezultata istraživanja koja su uključivala djecu i odrasle pokazuju da se djeca u usporedbi s odraslima psihički bolje nose s traumatskim iskustvima (18,19). U istraživanju Priebea i sur. osam godina nakon završetka rata anketirano je 3313 stanovnika i 854 izbjeglice iz pet balkanskih zemalja. Paranoidna ideacija i anksioznost u obama uzorcima bili su najteži psihički simptomi. Velik broj stresnih čimbenika povezanih s migracijom u skupini izbjeglica s privremenom dozvolom za boravak povezan je s većim općenitim stresnim opterećenjem i težim posttraumatskim stresnim sindromom (20). Sociodemografske značajke, iskustva iz rata i čimbenici stresa koji su povezani s migracijom neovisno su povezani s duševnim smetnjama i kod izbjeglica koje su već dulje nastanjene u državama domaćinima (21).

Izbjeglice često napuštaju svoju domovinu nakon što su izloženi događajima koji ugrožavaju život, kao što su ratni sukobi i nasilje. Možda su bili izloženi za ži-

vot opasnim situacijama i izbjeglištvom su riskirali zatvorsku kaznu ili gubitak voljene osobe. Izbjeglice mogu biti izložene progonu i represiji zbog svoje etničke pripadnosti, vjere ili seksualne orijentacije. U nekim državama još je uvijek dopušteno nasilje na osnovi spola, a i sakaćenje ženskih spolnih organa (22). Osim toga, izbjeglice prilikom dolaska u novu državu mogu utvrditi da su njihova očekivanja i predodžbe o razvijenom svijetu drugačije, zbog čega sve nade o boljem životu u trenutku nestanu (23).

ZAKLJUČAK

Migracije i globalizacija utječu na promjene u sastavu posjetitelja ambulanata na zdravstvenoj razini. Liječnici i ostalo zdravstveno osoblje u komunikaciji i liječenju migranata i izbjeglica moraju biti svjesni specifičnih čimbenika izvornih sociokulturnih okruženja. Jezične barijere trebalo bi pokušati premostiti uz pomoć tumača i kulturnih posrednika. Liječnici prilikom pružanja zdravstvene skrbi migrantima trebaju uzimati u obzir i specifične čimbenike stresa koji su povezani s migracijom i utječu na pojavnost duševnih smetnji i kad su migranti i izbjeglice dulje nastanjeni u državi domaćinu.

L I T E R A T U R A

1. Rodgers L, Gritten D, Offer J, Asare P. Syria: The story of the conflict. BBC News. Dohvaćeno 20. kolovoza 2016. na mrežnoj stranici: *www.bbc.com/news/world-middle-east-26116868*.

2. Priebe S, Sandhu S, Dias S i sur. Good practice in health care for migrants: views and experiences of care professionals in 16 European countries. BMC Public Health 2011; 178: 1-12.

3. Rechel B, Mladovsky P, Deville W, Rijks B, Petrova-Benedict R, McKee M. Migration and health in the European Union. Berkshire: Open University Press; 2011.

4. Alpern JD, Davey CS, Song J. Perceived barriers to success for resident physicians interested in immigrant and refugee health. BMC Med Educ, 2016; 16: 178.doi: 10.1186/s12909-016-0696-z

5. Terasaki G, Ahrenholz NC, Haider MZ. Care of adult refugees with chronic conditions. Med Clin North AM 2015; 99: 1039-58. Doi: 10.1016/j.mcna.2015.05.006.

6. Wachtler C, Brorsson A, Troein M. Meeting and treating cultural difference in primary care: a qualitative interview study. Fam Pract 2006; 23: 111-15.

7. Van Wieringen VCM, Harmsen JAM, Bruijnzeels MA. Intercultural communication in general practice. Eur J Pub Health 2002; 12: 63-6.

8. Ferguson WJ, Candib LM. Culture, language and the doctor-patient relationship. Fam Med 2002; 34: 353-61.

9. Bhatia R, Wallace P. Experiences of refugees and asylum seekers in general practice: a qualitative study. BMC Fam Pract 2007; 8: 48.

10. Berg JE, Smaland Goth UG. Migrant participation in Norwegian health care. A qualitative study using key informants. Eur J Gen Pract 2011; 17: 28-33.

11. Rocque R, Leanza Y. A Systematic Review of Patients Experiences in Communicating with Primary Care Physician: Intercultural Encounters and a Balance between Vulnerability and Integrity. PloS One 2015; 10: 10-34.

12. McCarthy A, Lee K, Itakura S, Muir DW. Cultural displays rules drive eye gaze during thinking. J Cross-Cultural Psychol 2006; 37: 717-22.

13. Bond MH, Komai H. Targets of gazing and eye contact during interviews: Effects on Japanese nonverbal behaviour. J Personality Social Psychol 1976; 34: 1276-84.

14. John-Baptiste A, Naglie G, Tomlinson G i sur. The effect of English language proficiency on length of stay and in-hospital mortality. J Gen Inter Med 2004; 19: 221-8.

15. Hudelson P, Vilpert S. Overcoming language barriers with foreign-language speaking patients: a survey to investigate intra-hospital variation in attitudes and practices. BMC Health Services Res 2009; 9: 6-8.

16. Lindholm M, Hargraves JL, Ferguson WJ, Reed G. Professional language interpretation and inpatient length of stay and readmission rates. J Gen Int Med 2012; 27: 1294-5.

17. Basic language emergency kit. Dohvaćeno 23. ožujka 2017. na mrežnoj stranici *www.takecareproject.eu/en-2*

18. Priebe S, Jankovic Gavrilovic J, Bremner S i sur. Psychological Symptoms as Long-Term Consequences of War Experiences. Psychopathology 2013;46: 45-54.

19. Reed RV, Fazel M, Jones L, Panter-Brick C, Stein A. Mental health of displaced and refugee children resettled in low-income and middle-income countries: risk and protective factors. Lancet 2012; 379: 250-65.

20. Bogic M, Ajdukovic D, Bremner S i sur. Factors associated with mental disorders in long-settled war refugees: refugees from the former Yugoslavia in Germany, Italy and the UK. Br J Psychiatry 2012; 200: 216-23.

21. Thomas S, Nafees B, Bhugra D. 'I was running away from death'- the pre-flight experiences of unaccompanied asylum seeking children in the UK. Child Care Health Dev 2004; 30: 113-22.

22. Janoff-Bulman R. Shattered Assumptions: Towards a New Psychology of Trauma. New York: Free Press; 1992.

23. Slobodin O, de Jong JT. Mental health interventions for traumatized asylum seekers and refugees: What do we know about their efficacy? Int J Soc Psychiatry 2015; 61: 17-26.

SUMMARY

COMMUNICATION OF DOCTOR WITH MIGRANTS AND REFUGEES

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Proper communication is crucial for successful treatment, and therefore it is an integral part of both undergraduate study and postgraduate training in medicine. The ability to communicate is very important in intercultural relations. When overcoming language barriers with migrants and refugees, physicians need to consider the patient socio-cultural beliefs, language barriers, and possible presence of latent infection and chronic diseases. Just as in medical examination of subjects from the majority population, communication should be individually adjusted when treating representatives of migrants and refugees. Thereby, it must be taken into account that non-verbal communication is not universal. For overcoming language barriers, physicians and health professionals mostly use services of lay interpreters who, in general, facilitate communication, but studies have shown that they may also have a negative role. Online translation tools, handbooks and dictionaries are used less frequently. Regardless of the patient cultural background and language barriers, the physician and his/her associates must build a trustful relationship based on mutual respect from the very beginning. When providing health care to migrants, physicians must take into account the specific stress factors associated with migration and their impact on the incidence of mental disorders, as well as long stays of migrants and refugees in the host country.

Key words: physician, health professional, refugee, migrant, communication, health care

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Suplement časopisa

Djelmiš J, Ivanišević M, Mrzljak A. Sadržaj lipida u placenti trudnica oboljelih od dijabetesa. Acta Med Croatica 2001; 55 (Supl. 1): 47-9.

Knjige i monografije

Mould RF. Introductory medical statistics. Turnbridge Wells: Pitman Medical, 1976.

Guluyer AY, ur. Health indicators. An international study for the European Science Foundation. Oxford: M. Robertson, 1983.

Poglavlje u knjizi

Weinstein I, Swartz MN. Pathogenic properties of invading microorganisms. U: Sodeman WA, ur. Pathologic physiology: mechanism of disease. Philadelphia: WB Saunders, 1974, 457-72.

Disertacija ili magistarski rad

Cigula M. Aktivnosti nekih enzima u humanom serumu kao pokazatelji apsorpcije žive (disertacija). Zagreb: Medicinski fakultet, 1987, str. 127.

Citiranje literature objavljene u elektroničkom formatu

Web

Hoffman DI, St John's Wort. 1995; [4 stranice]. Dostupno na URL adresi: http: //www.healthy.net/library/ books/hoffman/materiamedical/stjhns.htm. Datum pristupa informaciji: 16. srpnja 1998.

Morse SS. Factors in the emergence of infectious disease. Emrg Infect Dis [elektronički časopis na internetu] 1995; [24 ekrana/stranice] Dostupno na URL adresi: http: //www/cdcd/god/nsidoc/EID/eid.htm. Datum pristupa informaciji 26. prosinca 1999. Knjiga na CD-ROM-u

The Oxford English dictionary [knjiga na CD-ROMu]. II. izdanje. New York, N. Y: Oxford University Press, 1992.

Gershon ES. Antisocial behavior. Arch Gen Psychiatry [časopis na CD-ROM-u]. 1995; 52: 900-1.

Softver (program)

Epi Info [kompjutorski program]. Verzija 6. Atlanta, GA. Center for Disease Control and Prevention, 1994.

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Original papers s should contain: Introduction, Objective(s), Methods, Results, Discussion and Conclusions. In the Introduction section, the issue should be clearly and concisely presented. In Objective(s), the aim of the study is briefly described. In the Methods section, the methodology, apparatus and procedures used in the study should be identified in sufficient detail to allow other workers to reproduce the results. Widely known methods need not be described but original references should be used. For drugs, generic names should be used (trade names can be mentioned in parentheses). Results should be clearly and logically presented, and their significance should be demonstrated by appropriate statistical methods. In Discussion the results obtained are discussed against the existing state of the art. Conclusions should correspond with the aim(s) set in the Objective(s).

The title, first and last name(s) of the author(s), institution(s) and address of the corresponding author should be submitted on a separate sheet of paper. Synopsis written in Croatian should contain maximum 200 words on a separate sheet of paper.

Typescript should contain extended structured [Objective(s), Methods, Results, Discussion, Conclusion(s)] abstract (500-600 words) with title of the manuscript, initials of authors' first name(s), full last name(s) and institution(s) in English.

Below the Abstract, key words that will assist indexers in cross indexing the article should be provided.

Each table is presented on a separate sheet. Number tables consecutively in the order of their first citation in the text and supply a brief title for each. The same applies to figure legends. On the back of each figure put the name of the first author, the figure number and the «top», preferably with a soft pencil. Black-and-white glossy photographs should be submitted. Drawings should be made by Indian ink on white paper or printed by laser or ink jet printer using high resolution graphic techniques.

References are submitted on separate pages in the numbered sequence following their mention in the text. References are cited according to the «Vancouver style» proposed by the International Committee of Medical Journals Editors (N Engl J Med 1991; 324: 421-8 and BMJ 1991; 302: 338-41). The titles of journals should be abbreviated according to Index Medicus.

The manuscript must be accompanied by a statement on all authors' agreement on paper publication as well as on nonexistence of conflict of interest. *Article in the journal* (if where are six or less authors, they should all be mentioned; if there are seven or more authors, the first three should be mentioned and the «*et al*.» should be added.

Example: Smerdelj M, Pećina M, Hašpl M. Surgical treatment of infected knee contracture after war injury. Acta Med Croatica 2000; 53: 151-5.

Supplement

Djelmiš J, Ivanišević M, Mrzljak A. Sadržaj lipida u placenti trudnica oboljelih od dijabetesa. Acta Med Croatica 2001; 55 (Supl. 1): 47-9.

Books and monographs

Mould RF. Introductory medical statistics. Turnbridge Wells: Pitman Medical, 1976.

Guluyer AY, ur. Health indicators. An international study for the European Science Foundation. Oxford: M. Robertson, 1983.

Chapter (of a book)

Weinstein I, Swartz MN. Pathogenic properties of invading microorganisms. U: Sodeman WA, ur. Pathologic physiology: mechanism of disease. Philadelphia: WB Saunders, 1974, 457-72.

Disertation or MA Thesis

Cigula M. Aktivnosti nekih enzima u humanom serumu kao pokazatelji apsorpcije žive (disertacija). Zagreb: Medicinski fakultet, 1987, str. 127.

Citation of literature published in electronic format Web, Electronic journal, Book on CD-ROM, Journal on CD-ROM, Softver (program)

Examples done in Notes for Contributors in Croatian (preceding page).

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Sadržaj

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