UTICAJ INSULINSKE REZISTENCIJE NA TERAPIJSKI ODGOVOR KOD NOVODIJAGNOSTIKOVANIH BOLESNIKA SA MULTIPLIM MIJELOMOM

ORIGINALNI RAD

ORIGINAL ARTICLE

THE INFLUENCE OF INSULIN RESISTANCE ON THERAPEUTIC RESPONSE IN NEWLY DIAGNOSED PATIENTS WITH MULTIPLE MYELOMA

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SAŽETAK

Uvod: Prema rezultatima dosadašnjih istraživanja, ustanovljeno je da se disfunkcija *IGF* (engl. *insulin-like growth factor*) sistema, koja je u osnovi insulinske rezistencije sa hiperinsulinemijom, ponaša kao proliferatogeni tumorski faktor, a svoj neoplastični potencijal pokazuje i u multiplom mijelomu.

Cilj: Cilj studije je ispitivanje eventualne povezanosti insulinske rezistencije kod novodijagnostikovanih bolesnika obolelih od multiplog mijeloma (NDMM) sa postignutim terapijskim odgovorom nakon sprovedene indukcione hemioterapije.

Materijali i metode: Sprovedeno je prospektivno istraživanje koje je obuhvatilo 35 pacijenata sa NDMM-om (60% žena i 40% muškaraca), lečenih na Klinici za hematologiju Kliničkog centra Vojvodine. Vrednosti glikemije i insulinemije su određivane našte i postprandijalno a potom su izračunavane vrednosti *HOMA-IRI*n (našte) i *HOMA-IRI*pp (postprandijalno). Vrednosti *HOMA-IRI* > 2,2 su bile kriterijum za insulinsku rezistenciju. Analize su rađene u dva navrata – pre inicijalne hemioterapije i posle završenog lečenja. Procena terapijskog odgovora je sprovedena prema kriterijumima Srpske mijelomske grupe (SMG) i Međunarodne radne grupe za mijelom (engl. *International Myeloma Working Group – IMWG*). Statističke analize su sprovedene u *SPSS* programu (Verzija 22).

Rezultati: Bolesnici su bili prosečne starosti od 63,85 godina. Ukupno 86% bolesnika je povoljno odgovorilo na terapiju. Prosečna vrednost *HOMA-IRI*n pre terapije je bila 1,82 ± 0,79, a posle terapije 1,80 ± 0,72. Centralna vrednost medijane *HOMA-IRI*pp pre terapije je bila 5,46 sa interkvartalnim rasponom od 1,07 – 20,57, a posle terapije je bila 5,86 sa interkvartalnim rasponom od 1,22 – 28,22. Uočena je značajna negativna korelacija *HOMA-IRI*n nakon primenjene terapije i postignutog terapijskog odgovora ($p = 0,040$).

Zaključak: Aktivna konkomitantna terapija insulinske rezistencije kod NDMM-a bi mogla da unapredi odgovor na primenjenu antimijelomsku terapiju.

Ključne reči: hiperinsulinemija, multipli mijelom, terapijski odgovor

ABSTRACT

Introduction: According to the results of previous research, it was found that the dysfunction of the insulin-like growth factor (IGF) system, which is the basis of insulin resistance with hyperinsulinemia, acts as a proliferative tumor factor, and its neoplastic potential is also exhibited in multiple myeloma.

Study aim: The study aims to determine whether there is an association between insulin resistance in patients newly diagnosed with multiple myeloma (NDMM) and the achieved therapeutic response after induction chemotherapy.

Materials and methods: The prospective study included 35 NDMM patients (60% women and 40% men), treated at the Clinical Center of Vojvodina Clinic for Hematology. Glycemia and insulinemia levels were determined after fasting and postprandially, upon which the values of HOMA-IRIf (after fasting) and HOMA-IRIpp (postprandially) were calculated. HOMA-IRI values > 2.2 were the criteria for insulin resistance. The analyses were performed twice – before the initial chemotherapy and after the completion of the treatment. The therapeutic response was evaluated according to the criteria of the Serbian Myeloma Group (SMG) and the International Myeloma Working Group IMWG). Statistical analyses were performed in the SPSS program, Version 22.

Results: The average patient age was 63.85 years. In total, 86% of patients responded favorably to the therapy. The average value of HOMA-IRIf before treatment was 1.82 ± 0.79 and it was 1.80 ± 0.72 after therapy. The central median value of HOMA-IRIpp before treatment was 5.46, with an interquartile range of 1.07 – 20.57, and after treatment, it was 5.86 with an interquartile range of 1.22 – 28.22. A significant negative correlation between HOMA-IRIf after applied treatment and achieved therapeutic response was observed, ($p = 0.040$).

Conclusion: Active concomitant therapy of insulin resistance in NDMM could improve the response to applied antimyeloma treatment.

Keywords: hyperinsulinemia, multiple myeloma, therapeutic response

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UVOD

Multipli mijelom (MM) je maligna bolest iz grupe monoklonskih gamapatija sa ishodištem u koštanoj srži. Odlikuje se nekontrolisanom proliferacijom tumorski izmenjenih B-limfocita – plazmocita, koji produkuju patološki izmenjene imunoglobuline (M-protein). Ustanovljeno je da MM čini 1,8% svih malignih bolesti i 10% hematoloških maligniteta. U Evropi, godišnje oboli 4,5 – 6/100.000 stanovnika [1,2]. Smatra se bolešću starijeg životnog doba, uz veću učestalost u muškoj populaciji. Iako je postignut značajan napredak u lečenju MM-a u proteklih 20 godina, ova bolest je i dalje neizlečiva, te nedovoljno predvidivog toka i ishoda [3,4]. U cilju detekcije prognostičkog i terapijskog potencijala novih biohemijskih i molekularnih pokazatelja, neophodna su dalja dopunska istraživanja.

Insulinska rezistencija predstavlja otežano ili potpuno onemogućeno preuzimanje glukoze u periferna tkiva kod obolelog u odnosu na zdravu populaciju, što dovodi do porasta serumskog nivoa insulina, uz redukciju ekspresije insulinskih receptora na perifernim tkivima te posledični razvoj promena na postreceptorskom nivou [5]. Rezultati dosadašnjih istraživanja pokazuju da je uloga hiperinsulinemije i porasta bioraspoloživosti insulinskog faktora rasta 1 (engl. *insulin-like growth factor I – IGF-1*) u razvoju malignog procesa neosporna [6]. Potencijalni mehanizmi takvog epiloga su:

– moguća oštećenja DNK uz razvoj stečenih mutacija zbog povećane produkcije slobodnih kiseoničnih radikala
– promene na postreceptorskom nivou sa hiperstimulacijom brojnih ćelijskih signalnih puteva i uticaj na ćelijski metabolizam posredovan dejstvom insulinskih faktora rasta, što direktno stimuliše i ćelijsku proliferaciju [5].

Povišen serumski nivo insulina u jetri pojačava proizvodnju *IGF1*, a smanjuje sintezu proteina koji vezuju insulinske faktore rasta (engl. *insulin-like growth factor binding proteins 1 and 2 – IGFBP1 and IGFBP2*). Stimulativni efekat na rast tumora insulin može da ostvari direktnim dejstvom ili posredstvom uticaja *IGF-1*, sa posledičnim promitogenim i antiapoptotičnim dejstvom, kao što je prikazano na Slici 1 [6]. Tom prilikom, insulin prvo reaguje sa insulinskim receptorom (INSR), koji predstavlja integralni membranski protein i ima presudnu ulogu u formiranju biološkog odgovora ćelije na stimulaciju insulinom. Hiperekspresija INSR-a, dovodi do promene i biološkog odgovora ćelije na insulin sa uticajem na proliferaciju, sazrevanje i apoptozu. Ove promene mogu značajno doprineti neoplastičnoj transformaciji ćelije [6]. Osim direktnog vezivanja insulina, za INSR se mogu vezati i *IGF-1* i *IGF-2*, sa sličnim učinkom.

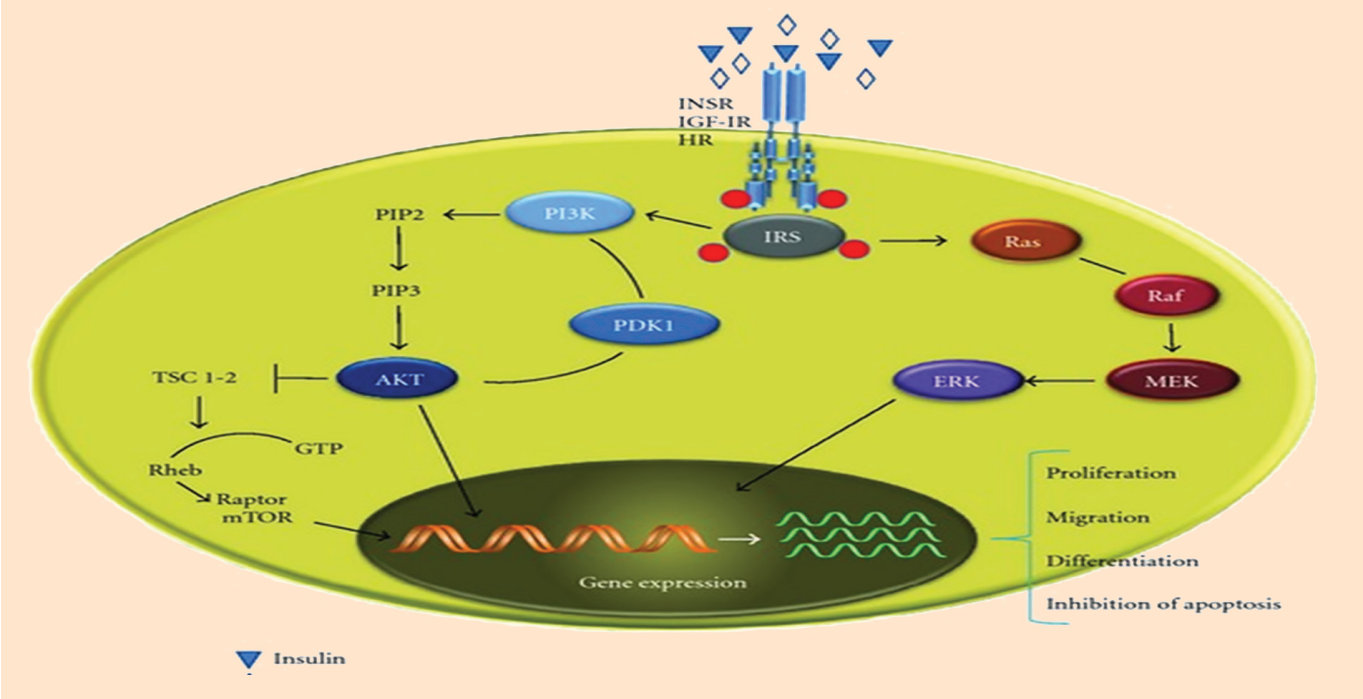
INTRODUCTION

Multiple myeloma (MM) is a malignant disease belonging to the group of monoclonal gammopathies originating in the bone marrow. It is characterized by the uncontrolled proliferation of tumorous B-lymphocytes – plasma cells, which produce pathologically altered immunoglobulins (M-protein). It was found that MM accounts for 1.8% of all malignant diseases and 10% of hematological malignancies. In Europe, 4.5 – 6/100,000 people are diagnosed annually [1,2]. Multiple myeloma is considered a disease of older age, with a higher frequency in the male population. Although significant progress has been made in the treatment of MM in the past 20 years, this disease is still incurable, and the course and outcome are insufficiently predictable [3,4]. In order to detect the prognostic and therapeutic potential of new biochemical and molecular indicators, further supplementary research is necessary.

Insulin resistance is impaired or completely incapacitated uptake of glucose into the peripheral tissues in patients affected by this condition, as compared to the healthy population, which leads to an increase in the serum level of insulin, with a reduction in the expression of insulin receptors in the peripheral tissues and the consequent development of changes at the post-receptor level [5]. The results of previous research show that the role of hyperinsulinemia and increased bioavailability of insulin-like growth factor 1 (IGF-1) in the development of the malignant process is undeniable [6]. Potential mechanisms of this are the following:

– possible DNA damage with the development of acquired mutations due to increased production of free oxygen radicals
– changes at the post-receptor level with hyperstimulation of numerous cell signaling pathways and the influence on cell metabolism mediated by the effect of insulin growth factors, which directly stimulates cell proliferation [5].

An elevated serum level of insulin in the liver increases the production of IGF1 and reduces the synthesis of insulin-like growth factor binding proteins 1 and 2 - IGFBP1 and IGFBP2. Insulin can stimulate tumor growth directly or through the influence of IGF-1, with a consequent promitogenic and antiapoptotic effect, as shown in Figure 1 [6]. In this case, insulin first reacts with the insulin receptor (INSR), which is an integral membrane protein and plays a crucial role in the formation of the cell's biological response to insulin stimulation. Hyperexpression of INSR leads to a change in the biological response of the cell to insulin with an impact on proliferation, maturation, and apoptosis. These changes can significantly contribute to the neoplastic transformation of the cell [6]. In addition to direct insu-



Slika 1. Prikaz efekta stimulacije INSR-a i pokretanja kaskade signalnih puteva koji su u osnovi biološkog odgovora ćelije na insulin (preuzeto uz dopuštenje izdavača) [6]
https://www.ncbi.nlm.nih.gov/pmc/articles/instance/3372318/bin/EDR2012-789174.003.jpg

Picture 1. Presentation of the effect of INSR stimulation and the initiation of the cascade of signaling pathways underlying the biological response of the cell to insulin (reproduced with permission of the publisher) [6]
https://www.ncbi.nlm.nih.gov/pmc/articles/instance/3372318/bin/EDR2012-789174.003.jpg

I pored brojnih istraživanja koja su do sada sprovedena, posredovanje insulinske rezistencije u karcinogenezi nije rasvetljeno na način koji bi omogućio i trasirao nove dijagnostičke i terapijske modalitete sa ciljem prevencije maligniteta, ili u slučaju već prisutne maligne bolesti, sa ciljem poboljšanja toka, odgovora na terapiju i ishoda lečenja [7].

CILJ

Cilj istraživanja je bio da se utvrdi da li postoji povezanost insulinske rezistencije kod novodijagnostikovanih bolesnika obolelih od multiplog mijeloma (NDMM) sa postignutim terapijskim odgovorom nakon sprovedene indukcione hemioterapije.

MATERIJALI I METODE

Istraživanje je sprovedeno u periodu od 2017. do 2021. godine na Klinici za hematologiju Univerzitetskog kliničkog centra Vojvodine, a nakon dobijene saglasnosti Etičkog odbora. Obuhvatilo je 35 novodijagnostikovanih bolesnika sa multiplim mijelomom, starosti 18 –85 godina, koji do trenutka uključivanja u ovo prospektivno istraživanje nisu primili nikakvu antimijelomsku terapiju. Takođe, ispitanici nisu koristili ni lekove sa uticajem na insulinsku senzitivnost, produkciju i lučenje insulina (oralni hipoglikemici na bazi metformina, derivati sulfonilureje, tiazolindioni, *SGLT-2* inhibitori,

lin binding, IGF-1 and IGF-2 can also bind to INSR, with a similar effect.

Notwithstanding the numerous studies carried out so far, the mediation of insulin resistance in carcinogenesis has not been elucidated in a way that would allow for and establish new diagnostic and therapeutic modalities to prevent malignancy, or in the case of already existing malignant disease, to improve the course, response to therapy and treatment outcomes [7].

STUDY AIM

The study aimed to determine whether there is a connection between insulin resistance in patients newly diagnosed with multiple myeloma (NDMM) and the achieved therapeutic response after induction chemotherapy.

MATERIALS AND METHODS

The research was conducted between 2017 and 2021 at the Clinic for Hematology of the University Clinical Center of Vojvodina, after obtaining the consent of the Ethics Committee. It included 35 patients newly diagnosed with multiple myeloma, aged 18 – 85 years, who had not received any anti-myeloma therapy until the time of inclusion into this prospective study. Also, the subjects did not use drugs with an impact on insulin sensitivity, insulin production, and insulin secretion

GLP1-R agonisti, insulinska terapija), kao ni hipolipidemike sa uticajem na insulinsku senzitivnost (statini, fibrati). Dokazana druga maligna bolest je bila kriterijum za isključivanje iz studije.

U uvodnoj fazi istraživanja, nakon obavljenog razgovora, ispitanici su fizički pregledani a potom su urađene i biohemijske, dopunske hematološke i radiološke analize predviđene protokolom Srpske mijelomske grupe (SMG) za inicijalno određivanja stadijuma NDMM-a [4].

Dopunske hematološke i biohemijske analize su obuhvatale određivanje kompletne krvne slike (KKS), parametara bubrežne funkcije (urea, kreatinin, klirens kreatinina u 24-h urinu) i aktivnosti osnovne bolesti (serumska koncentracija laktat dehidrogenaze (LDH), beta-2-mikroglobulin (β2M), elektroforeza serumskih proteina (EFSP), serumska koncentracija imunoglobulina IgA, IgM i IgG, serumska koncentracija slobodnih lakih lanaca (SLL) κ i λ, imunofiksacija proteina u serumu i 24-h urinu), kao i standardnih inflamatornih parametara (brzina sedimantacije eritrocita (SE), C-reaktivni protein (CRP)).

U cilju procene insulinske rezistencije, merene su vrednosti glikemije i insulinemije našte i postprandijalno (2 h posle obroka), koje su dalje izračunavane prema datoj formuli: glikemija našte (mmol/l) x insulinemija našte (mIU/l) / 22,5, kako bi se odredila vrednost HOMA-IRI (engl. homeostatic model assessment-insulin resistance index) [8]. Vrednosti HOMA-IRI > 2,2 su bile kriterijum za dijagnozu insulinske rezistencije [9]. Određivane su vrednosti HOMA-IRIn (našte) i HOMA-IRIpp (postprandijalno, provocirano, gde su kalkulisane vrednosti glikemije i insulinemije 2 h nakon obroka).

Sve analize su rađene u dva vremena: pre započinjanja terapije i nakon završenog lečenja bolesnika. Terapijski odgovor je procenjivan prema važećim kriterijumima SMG i Međunarodne radne grupe za mijelom (engl. International Myeloma Working Group – IMWG), kao što je prikazano u Tabeli 1, i kvalifikovan kao: čvrsta kompletna remisija (engl. stringent complete remission – sCR), kompletna remisija (engl. complete remission – CR), veoma dobar parcijalni odgovor (engl. very good partial response – VGPR), parcijalna remisija (engl. partial remission – PR), stabilna bolest (engl. stable disease – SDi), progresija bolesti (engl. progressive disease – PD) [10].

Za svakog pacijenta su iz baze podataka prikupljeni longitudinalni podaci iz dve vremenske tačke: pre ulaska u proces hemioterapije i posle lečenja indukcionom hemioterapijom, nakon šest do sedam terapijskih ciklusa.

Same statističke analize su sprovedene u SPSS (Verzija 22) statističkom paketu, a grafički prikazi su tran-

(oral hypoglycemics based on metformin, sulfonylurea derivatives, thiazolidinediones, SGLT-2 inhibitors, GLP1-R agonists, insulin therapy), nor hypolipidemic drugs with an impact on insulin sensitivity (statins, fibrates). Another proven malignancy in a patient was an exclusion criterion.

In the initial phase of the study, after the doctor-patient interview, the subjects were physically examined, upon which biochemical, additional hematological, and radiological analyses were performed, as specified by the protocol of the Serbian Myeloma Group (SMG) for initially determining the stage of NDMM [4].

Additional hematological and biochemical analyses included the complete blood count (CBC), kidney function tests (urea, creatinine, creatinine clearance in 24-h urine collection), tests related to the activity of the underlying disease (serum level of lactate dehydrogenase (LDH), serum level of beta-2-microglobulin (β2M), serum protein electrophoresis (SPEP), serum levels of immunoglobulins IgA, IgM, and IgG, serum levels of free light chains (FLC) κ and λ, serum immunofixation test, and 24-h urine collection), as well as standard inflammatory markers (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)).

To assess insulin resistance, fasting and postprandial glycemia and insulinemia values were measured, which were further calculated according to the given formula: fasting glycemia (mmol/l) x fasting insulinemia (mIU/l) / 22.5, to calculate the value of the homeostatic model assessment-insulin resistance index (HOMA-IRI) [8]. HOMA-IRI values > 2.2 were the criterion for diagnosing insulin resistance [9]. The values of HOMA-IRIf (fasting HOMA-IRI) and HOMA-IRIpp (postprandial, provoked, where the values of glycemia and insulinemia were calculated 2 h after the meal) were calculated.

All tests were performed at two points in time: before starting the therapy and after the patient's treatment was completed. The therapeutic response was evaluated according to the valid SMG and International Myeloma Working Group (IMWG) criteria, as shown in Table 1, and qualified as follows: stringent complete remission (sCR), complete remission (CR), very good partial response (VGPR), partial remission (PR), stable disease (SDi), disease progression (PD) [10].

For each patient, longitudinal data were collected from the database for two points in time: before entering the chemotherapy process and after treatment with induction chemotherapy, after six to seven treatment cycles.

The statistical analyses were carried out in the SPSS (Version 22) statistical package, and the graphical representations were transposed into the Excel

Tabela 1. Klasifikacija odgovora na primenjenu terapiju, MM

Table 1. Classification of response to administered therapy, MM

sCR	✓ Odsustvo monoklonskih plazma ćelija u koštanoj srži / *Absence of monoclonal plasma cells in the bone marrow* ✓ Odsustvo M komponente u imunofiksaciji proteina u serumu i 24-h urinu / *Absence of the M component in serum immunofixation and in 24-h urine collection* Normalan SLLκ/SLLλ / *Normal serum FLCκ/FLCλ*
CR	✓ < 5% monoklonskih plazma ćelija u koštanoj srži / *< 5% of monoclonal plasma cells in the bone marrow* ✓ Odsustvo M komponente u imunofiksaciji proteina u serumu i 24-h urinu / *Absence of the M component in serum immunofixation and in 24-h urine collection* Normalan SLLκ/SLLλ / *Normal serum FLCκ/FLCλ*
VGPR	✓ munofiksacijom detektabilan M protein u serumu i 24-h urinu / *Serum and urine M-protein detectable by immunofixation and in 24-h urine collection* ✓ Redukcija M proteina u EFSP za > 90% / *> 90% reduction in serum M-protein in EPSP* M protein < 100 mg u 24-h urinu / *M protein < 100 mg in 24-h urine collection*
PR	✓ M protein u serumu snižen za ≥ 50% / *≥ 50% reduction of serum M-protein* ✓ M protein u 24-h urinu snižen za ≥ 90%, ili proteinurija u 24-h urinu < 200 mg / *M protein in 24-h urine collection reduced by ≥ 90%, or proteinuria in 24-h urine collection < 200 mg* ✓ Ukoliko je M protein u serumu i urinu nemerljiv, potrebno je da je SLLκ/λ smanjen za ≥ 50% / *If the serum and urine M-protein are unmeasurable, it is required that serum FLCκ/λ is reduced by ≥ 50%* ✓ Redukcija infiltracije koštane srži za > 50%, ako je M protein u serumu i urinu nemerljiv i ako su laki lanci nemerljivi / *Reduction of bone marrow infiltration by > 50%, if the serum and urine M-protein are unmeasurable and if light chains are unmeasurable* ✓ Redukcija mekotkivnih infiltrata za ≥ 50% / *Reduction of soft tissue infiltrates by ≥ 50%*
SDi	Bez kriterijuma za *CR, VGPR, PR, PD / Not meeting criteria for CR, VGPR, PR, or PD*
PD	✓ Porast M proteina u serumu (apsolutni porast ≥ 0,5 g/dl) i/ili / *Increase of serum M-protein (absolute increase ≥ 0,5 g/dl) and/or* ✓ Porast M proteina u urinu (apsolutni porast ≥ 200 mg/24 h) / *Increase of urine M-protein (absolute increase ≥ 200 mg/24 h)*

Legenda: *sCR* – čvrsta kompletna remisija (engl. *stringent complete remission*), *CR* –kompletna remisija (engl. *complete remission*), *VGPR* – veoma dobar parcijalni odgovor (engl. *very good partial response*), *PR* – parcijalna remisija (engl. *partial remission*), *SDi* – stabilna bolest (engl. *stable disease*), *PD* – progresija bolesti (engl. *progressive disease*)

Legend: sCR – stringent complete remission, CR – complete remission, VGPR – very good partial response, PR – partial remission, SDi – stable disease, PD – progressive disease

sponovani u Excel format, radi bolje preglednosti. U cilju prikaza deskriptivnih pokazatelja i frekvencijske raspodele, korišćena je deskriptivna statistika, odnosno standardni deskriptivni statistički pokazatelji: aritmetička sredina, standardna devijacija, koeficijent zakošenosti distribucije (engl. skewness) i koeficijent spljoštenosti distribucije (engl. curtosis), a za varijable koje se ne distribuiraju po normalnoj raspodeli prikazani su medijana i raspon, kao deskriptivni parametri. T-test za zavisne uzorke i Vilkoksonov test predznaka su korišćeni u cilju ukazivanja na promene parametara pre i posle indukcione hemioterapije, u zavisnosti od toga da li su analizirane normalno distribuirane varijable ili varijable koje ne prate normalnu raspodelu podataka. Međusobne relacije varijabli ispitane su putem Spirmanovog koeficijenta korelacije, s obzirom na to da postignut terapijski odgovor u ovom istraživanju predstavlja varijablu ordinalnog nivoa merenja. Statističke hipoteze su testirane na nivou statističke značajnosti (alfa nivo) od 0,05.

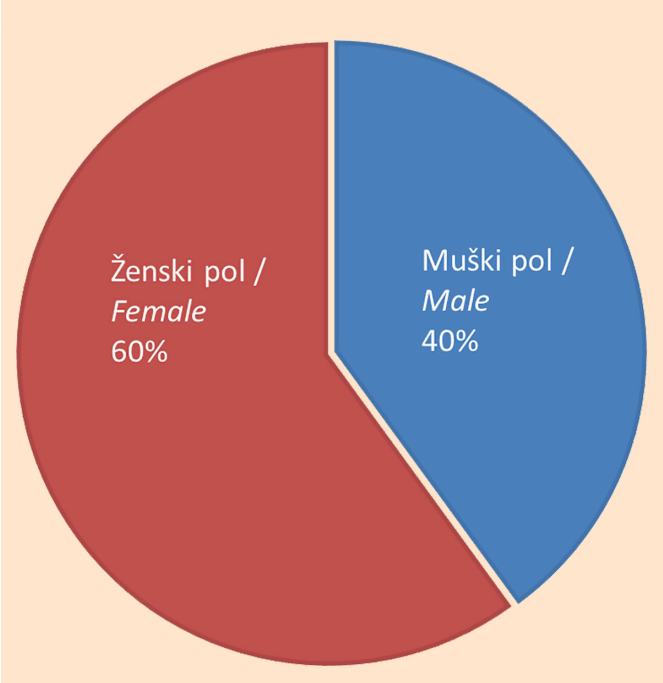
format for better visibility. In order to display descriptive indicators and frequency distribution, descriptive statistics were used, i.e. standard descriptive statistical indicators: arithmetic mean, standard deviation, skewness, and kurtosis, and for variables not distributed according to the normal distribution, median and range were presented as descriptive parameters. The t-test for dependent samples and the Wilcoxon signed-rank test were used to indicate changes in parameters before and after induction chemotherapy, depending on whether normally distributed variables or non-normally distributed variables were analyzed. Interrelationships of the variables were examined using the Spearman correlation coefficient, given that the achieved therapeutic response in this study was an ordinal variable. Statistical hypotheses were tested at a statistical significance level (alpha level) of 0.05.

RESULTS

The sex ratio of newly diagnosed patients with multiple myeloma was as follows: 60% women and 40%

REZULTATI

Kada je u pitanju polna struktura novodijagnostikovanih bolesnika obolelih od multiplog mijeloma, bilo je



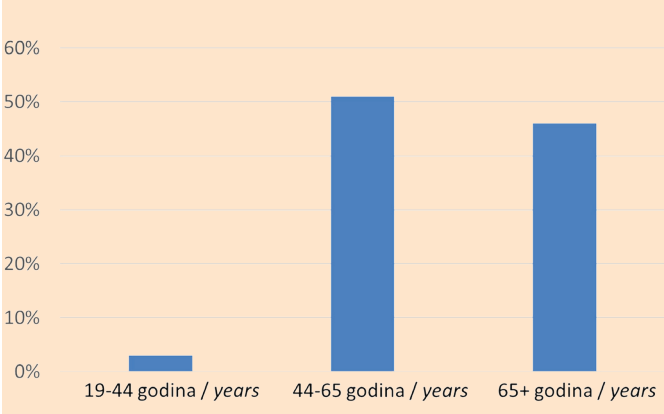
Grafikon 1. Polna struktura ispitanika u MM grupi

Graph 1. Male to female ratio in the MM group

60% žena i 40% muškaraca (Grafikon 1), ali ova razlika nije bila statistički značajna ($p = 0{,}320$). Ispitanici su bili prosečne starosti od 63,85 godina. Detektovane su statistički značajne razlike u strukturi ispitanika u odnosu na starosne grupe ($p < 0{,}001$). Svega 3% ispitanika je bilo starosti 19 – 41 godina, a 51% ispitanika je bilo uzrasta 45 – 65 godina (podaci prikazani u Grafikonu 2). Iako je čak 60% NDMM ispitanika bilo u III kliničkom stadijumu, heterogenost ispitanika u odnosu na ovu ispitivanu varijablu nije bila statistički značajna ($p = 0{,}200$).

Nakon sprovedene indukcione hemioterapije je, prema Grafikonu 3, čak 86% ispitanika ostvarilo je odgovor na terapiju: 6% CR, 40% PR i 40% VGPR. Prosečna vrednost HOMA-IRIn je pre terapije bila 1,82 ± 0,79 a posle terapije 1,80 ± 0,72. Prosečna vrednost HOMA-IRIpp je i pre i posle primenjene terapije ispunjavala kriterijume za insulinsku rezistenciju (HOMA-IRIpp ≥ 2,2). Centralna vrednost medijane HOMA-IRIpp je pre terapije bila 5,46 sa interkvartalnim rasponom 1,07 – 20,57, a posle terapije je bila 5,86 sa interkvartalnim rasponom 1,22 – 28,22. Nakon sprovedenog lečenja, nije detektovano statistički značajno smanjenje vrednosti, HOMA-IRIn ($p = 0{,}792$) i HOMA-IRIpp ($p = 0{,}864$). Podaci su prikazani u Tabeli 2.

men (Chart 1), however, this difference was not statistically significant ($p = 0.320$). The average age of the respondents was 63.85 years. Statistically significant differences were detected in the structure of respon-

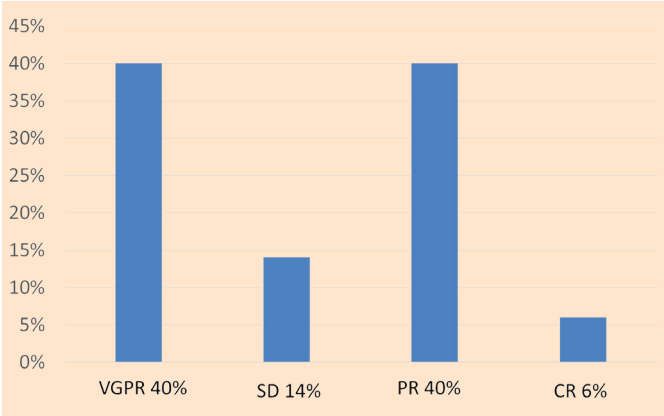


Grafikon 2. Distribucija ispitanika po starosnim intervalima u MM grupi

Graph 2. Respondent distribution by age intervals in the MM group

dents in relation to age groups ($p < 0.001$). Only 3% of respondents were aged 19 – 41 years, and 51% of respondents were aged 45 – 65 years (data presented in Graph 2). Although as many as 60% of NDMM subjects were in clinical stage III, the heterogeneity of the subjects regarding this variable was not statistically significant ($p = 0.200$).

After induction chemotherapy, according to Graph 3, as many as 86% of subjects achieved a response to treatment: 6% CR, 40% PR, and 40% VGPR. The average value of HOMA-IRIf before treatment was 1.82 ± 0.79 and after treatment, it was 1.80 ± 0.72. The average value of HOMA-IRIpp both before and after the applied therapy met the criteria for insulin resistance



Grafikon 3. Prikaz postignutih odgovora na primenjenu terapiju u MM grupi ispitanika

Graph 3. Presentation of achieved therapeutic response in the MM respondent group

Tabela 2. Deskriptivni prikaz HOMA-IRIn i HOMA-IRIpp kod ispitivanih NDMM bolesnika

Table 2. Descriptive presentation of HOMA-IRIf and HOMA-IRIpp in the analyzed NDMM patients

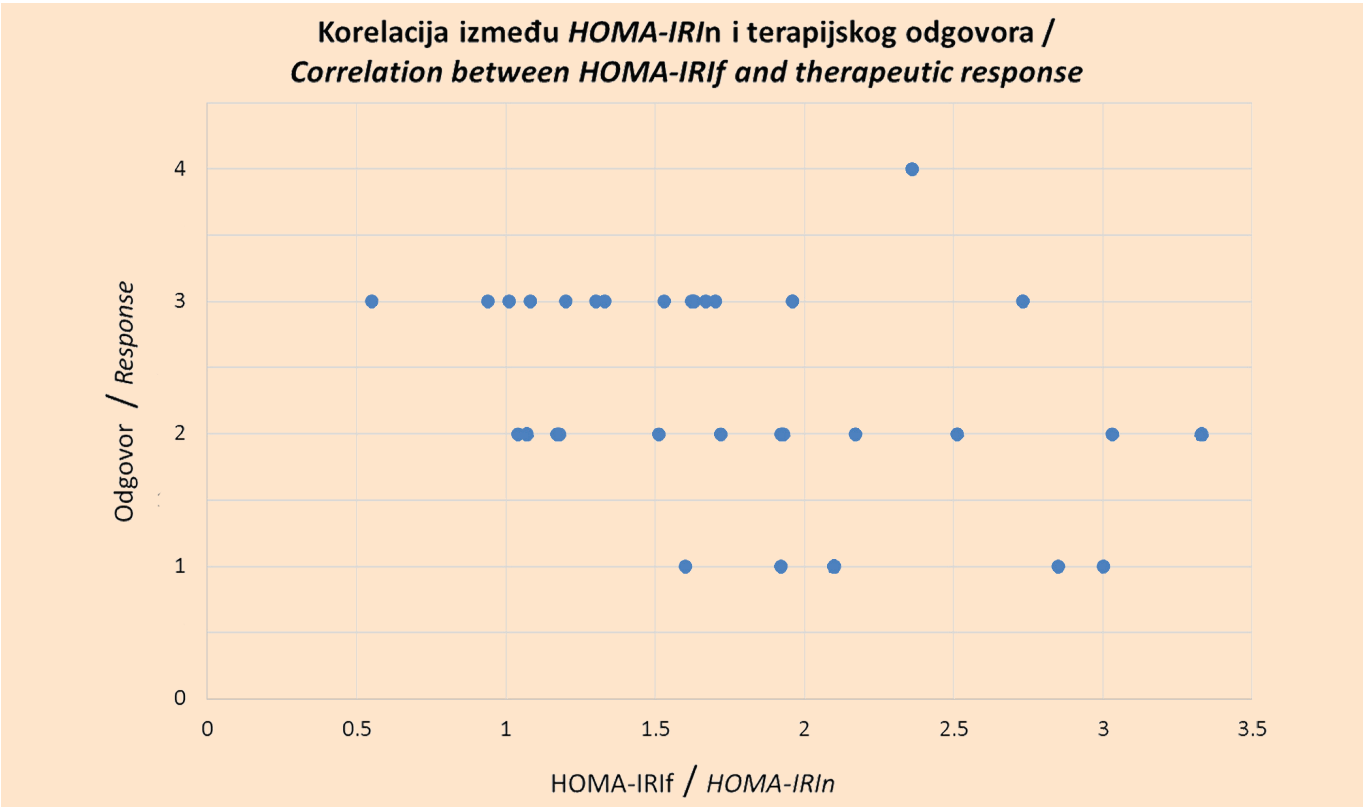
	Pre terapije / *Before treatment*			Posle terapije / *After treatment*			*p*
	M ± SD	Sk	Ku	M ± SD	Sk	Ku	
HOMA-IRIn / *HOMA-IRIf*	1.82 ± 0.79	0.70	0.35	1.80 ± 0.72	0.61	-0.2	0.792
	Mdn	Min	Max	Mdn	Min	Max	*p*
HOMA-IRIpp / *HOMA-IRIpp*	5.46	1.07	20.57	5.86	1.22	28.22	0.864

Legenda: *M* – aritmetička sredina (engl. *mean*), SD – standardna devijacija, *Sk* – koeficijent zakošenosti distribucije (engl. *skewness*), *Ku* – koeficijent spljoštenosti distribucije (engl. *kurtosis*), Mdn – medijana, Min – minimalna vrednost, Maks – maksimalna vrednost, p – nivo značajnosti

Legend: M – mean, SD – standard deviation, Sk – skewness, Ku – kurtosis, Mdn – median, Min – minimum, Max – maximum, p – level of significance

Daljim analizama je potvrđena negativna korelacija ostvarenog terapijskog odgovora i vrednosti insulinske rezistencije našte, izmerene nakon sprovedenog lečenja. Naime, više vrednosti *HOMA-IRI*n izmerene posle sprovedenog lečenja impliciraju i lošiji terapijski odgovor ($p = 0{,}040$), kao što je i prikazano u Grafikonu 4.

(HOMA-IRIpp ≥ 2.2). The central median value of HOMA-IRIpp before treatment was 5.46 with an interquartile range of 1.07 - 20.57, and after treatment, it was 5.86 with an interquartile range of 1.22 - 28.22. After the treatment, no statistically significant decrease in HOMA-IRIf ($p = 0.792$) and HOMA-IRIpp ($p = 0.864$) values was detected. The data are presented in Table 2.



Grafikon 4. Prikaz negativne Spirmanove korelacije HOMA-IRIn i postignutog terapijskog odgovora kod NDMM

Graph 4. Presentation of the negative Spearman correlation of HOMA-IRIf and achieved therapeutic response in NDMM

DISKUSIJA

Istraživanje insulinske rezistencije kod nedijabetesne populacije NDMM bolesnika je sprovedeno sa planom evaluacije njenog eventualnog prognostičkog značaja, kao i mogućeg uticaja na tok i ishod lečenja. Iako je verifikovana inicijalno očuvana insulinska senzitivnost kod naših NDMM bolesnika, izračunate prosečne vrednosti *HOMA-IRI*pp, pre i nakon sprovedenog lečenja, bile su u kategoriji provocirane insulinske rezistencije. Takođe, detektovana je negativna korelacija insulinske rezistencije nakon primenjene terapije i postignutog terapijskog odgovora. Lošiji odgovor na terapiju su imali bolesnici sa višim izračunatim vrednostima *HOMA-IRI*n nakon sprovedenog lečenja. NDMM bolesnici sa ostvarenim boljim odgovorom na primenjenu terapiju su imali niži *HOMA-IRI*n. Može se reći da niže *HOMA-IRI* vrednosti kod NDMM bolesnika ukazuju na veću verovatnoću remisije, kao i manju mogućnost izostanka odgovora na terapiju ili progresije pod terapijom. Ovakvi rezultati bi svakako i mogli biti očekivani, imajući u vidu do sada već detektovanu metaboličku vulnerabilnost multiplog mijeloma, čiji je glavni akter takozvani *IGF* (engl. *insulin-like growth factor*) sistem [11,12]. Ovaj sistem se sastoji iz sledećeg: dva faktora rasta – *IGF1* i *IGF2*, dva receptora – *IGF1* receptor (*IGF1R*) i *IGF2* receptor (*IGF2R*), *IGFBP*, *IGFBP* proteaze [11]. Važno je napomenuti da su *IGF1* i *IGF2* peptidi koji se strukturno u velikoj meri preklapaju sa građom proinsulina, a dosadašnjim istraživanjima je dokazan i njihov uticaj na životni vek i proliferativni indeks plazmocita, angiogenezu i aktivnost osteoklasta [13,14,15]. Visok stepen preklapanja je detektovan i u strukturi insulina i *IGF*, tako da *IGF* sistem može biti i direktno uključen u regulaciju homeostaze glukoze, vezivanjem za insulinske receptore [11,16]. Disfunkcija *IGF* sistema pogoduje razvoju insulinske rezistencije i porastu serumskog nivoa insulina dovodeći do „prezasićenosti" insulinskih receptora *IGF1* i *IGF2* uz konsekventne promene i na postreceptorskom nivou, stimulišući proliferaciju plazmocita i progresiju bolesti [13,17]. Samim tim se nameće zaključak da bi insulinski receptori mogli biti pogodne biološke mete za razvoj novih modaliteta u lečenju MM-a [18,19]. Drugi zaključak bi bio da se primena humanog insulina u dijabetesnoj mijelomskoj populaciji može razmatrati kao potencijalni faktor koji doprinosi progresiji MM [19,20].

Imajući u vidu i mehanizam kojim svoje dejstvo ostvaruje peroralni antidijabetesni lek, metformin, modulacijom *INSR/IGF1R* signalnog puta, može se razmatrati i antitumorski efekat ovog leka, koji je osvedočen rezultatima brojnih dosadašnjih istraživanja [14,15]. Boursi i saradnici su u svom prospektivnom istraživanju pokazali da primena metformina kod dijabetičara

Further analyses confirmed the negative correlation between the achieved therapeutic response and fasting insulin resistance values, measured after the treatment. Namely, higher values of HOMA-IRIf measured after treatment imply a poorer therapeutic response ($p = 0.040$), as shown in Graph 4.

DISCUSSION

The analysis of insulin resistance in the non-diabetic population of NDMM patients was conducted to evaluate its possible prognostic significance, as well as its possible influence on the course and outcome of treatment. Although initially preserved insulin sensitivity was verified in our NDMM patients, the calculated average values of HOMA-IRIpp, before and after the treatment, were in the category of provoked insulin resistance. Also, a negative correlation of insulin resistance after applied therapy and achieved therapeutic response was detected. Patients with higher calculated HOMA-IRIf values after treatment had a poorer response to therapy. NDMM patients with a better response to the applied therapy had a lower HOMA-IRIf. It can be said that lower HOMA-IRI values in NDMM patients indicate a higher probability of remission, as well as a lower possibility of no response to therapy or progression under therapy. Such results could certainly be expected, bearing in mind the already detected metabolic vulnerability of multiple myeloma, whose main agent is the IGF (insulin-like growth factor) system [11,12]. This system consists of the following: two growth factors - IGF1 and IGF2, two receptors - IGF1 receptor (IGF1R) and IGF2 receptor (IGF2R), and IGFBP protease [11]. It is important to note that IGF1 and IGF2 are peptides that structurally overlap, to a great extent, with the structure of proinsulin, and previous research has proven their influence on the lifespan and proliferative index of plasma cells, angiogenesis, and osteoclast activity [13,14,15]. A high degree of overlap was detected in the structure of insulin and IGF, therefore, the IGF system may be directly involved in glucose homeostasis regulation, by binding to insulin receptors [11,16]. Dysfunction of the IGF system favors the development of insulin resistance and an increase in serum insulin levels, leading to the "oversaturation" of insulin receptors with IGF1 and IGF2, consequently bringing about changes at the post-receptor level, stimulating the proliferation of plasma cells and disease progression [13,17]. This leads to the conclusion that insulin receptors could be suitable biological targets for developing new modalities in the treatment of MM [18,19]. Another conclusion would be that the administration of human insulin in the diabetic myeloma population can be considered as a potential factor contributing to the progression of MM [19,20].

obolelih od monoklonske gamapatije neodređenog značaja (engl. *monoclonal gammopathy of undetermined significance – MGUS*), značajno redukuje rizik od progresije bolesti u multipli mijelom [21]. Antitumorski učinak metformina u populaciji obolelih od monoklonske gamapatije su u svom istraživanju potvrdili i Papahristu i saradnici, sa idejom o proširenju istraživanja i na nedijabetesnu populaciju [22]. Efikasnost primene metformina u nedijabetesnoj populaciji obolelih od *MGUS*-a, sa procenom smanjenja rizika od progresije bolesti u aktivnu formu MM, trenutno je predmet istraživanja kliničke studije *NCT04850846*, čiji rezultati tek treba da budu objavljeni [23].

ZAKLJUČAK

S obzirom da istraživanja sprovedena u proteklih desetak godina svedoče o izraženoj metaboličkoj osetljivosti multiplog mijeloma, ne iznenađuje ni nepovoljan učinak insulinske rezistencije na ostvareni terapijski odgovor. U skladu sa tim bi i aktivan konkomitantni terapijski pristup u zbrinjavanju insulinske rezistencije i prateće hiperinsulinemije – inicijalne i/ili provocirane, u nedijabetesnoj populaciji NDMM bolesnika, bio nezanemarljiv doprinos u ostvarivanju povoljnijeg odgovora na standardnu antimijelomsku terapiju.

SKRAĆENICE

β2M – beta-2-mikroglobulin
CR – kompletna remisija (engl. *complete remission*)
CRP – C-reaktivni protein
EFSP – elektroforeza serumskih proteina
GLP1-R – glukagonu slični peptid-1 receptor (engl. *glucagon-like peptide-1 receptor*)
HOMA-IRI – engl. *homeostatic model assessment-insulin resistance index*
*HOMA-IRI*n – *homeostatic model assessment-insulin resistance index,* našte
*HOMA-IRI*pp – *homeostatic model assessment-insulin resistance index,* postprandijalno
IMWG – Međunarodna radna grupa za mijelom (engl. *International Myeloma Working Group*)
INSR – insulinski receptor
Ku – koeficijent spljoštenosti distribucije (engl. *kurtosis*)
LDH – laktat dehidrogenaza
M – aritmetička sredina (engl. *mean*)
Maks – maksimalna vrednost
Mdn – medijana
MM – multipli mijelom
MGUS – monoklonska gampatija neodređenog značaja (engl. *monoclonal gammopathy of undetermined significance*)
Min – minimalna vrednost
NDMM – novodijagnostikovani multipli mijelom
PR – parcijalna remisija (engl. *partial remission*)
PD – progresija bolesti (engl. *progressive disease*)
SD – standardna devijacija

Bearing in mind the mechanism whereby the oral antidiabetic drug metformin achieves its effect by modulating the INSR/IGF1R signaling pathway, the antitumor effect of this drug, proven by the results of numerous previous studies, should also be considered [14,15]. In their prospective study, Boursi et al. demonstrated that the application of metformin in diabetic patients with monoclonal gammopathy of undetermined significance (MGUS) significantly reduces the risk of disease progression to multiple myeloma [21]. The antitumor effect of metformin in the population of patients with monoclonal gammopathy was confirmed in their research by Papachristou et al., with the idea of extending the research to the non-diabetic population as well [22]. The effectiveness of metformin administration in the non-diabetic population of MGUS patients, with an assessment of the reduction in the risk of disease progression to active MM, is currently the subject of research in the clinical study NCT04850846, whose results have yet to be published [23].

CONCLUSION

Given that research conducted in the past ten years testifies to the pronounced metabolic sensitivity of multiple myeloma, the adverse effect of insulin resistance on the achieved therapeutic response is not surprising. Accordingly, an active concomitant therapeutic approach in treating insulin resistance and accompanying hyperinsulinemia – initial and/or provoked, in the non-diabetic population of NDMM patients, would be a significant contribution to achieving a more favorable response to standard antimyeloma therapy.

ABBREVIATIONS AND ACRONYMS

β2M – beta-2-microglobulin
CR – complete remission
CRP – C-reactive protein
EPSP – serum protein electrophoresis
GLP1-R – glucagon-like peptide-1 receptor
HOMA-IRI – homeostatic model assessment-insulin resistance index
HOMA-IRIf – homeostatic model assessment-insulin resistance index, after fasting
HOMA-IRIpp – homeostatic model assessment-insulin resistance index, postprandially
IMWG – International Myeloma Working Group
INSR – insulin receptor
Ku – kurtosis
LDH – lactate dehydrogenase
M – mean
Maks – maximum
Mdn – median
MM – multiple myeloma
MGUS – monoclonal gammopathy of undetermined significance

SDi – stabilna bolest (engl. *stable disease*)
Sk – koeficijent zakošenosti distribucije (engl. *skewness*)
SGLT 2 – (engl. *sodium-glucose cotransporter 2*)
SLL*κ* – slobodni laki lanci kapa
SLLλ – slobodni laki lanci lambda
SMG – Srpska mijelomska grupa
sCR – čvrsta kompletna remisija (engl. *stringent complete remission*)
VGPR – veoma dobar parcijalni odgovor (engl. *very good partial response*)

Sukob interesa: Nije prijavljen.

Min – minimum
NDMM – newly diagnosed multiple myeloma
PR – partial remission
PD – progressive disease
SD – standard deviation
SDi – stable disease
Sk – skewness
SGLT 2 – sodium-glucose cotransporter 2
FLCκ – kappa free light chains
FLCλ – lambda free light chains
sCR – stringent complete remission
SMG – Serbian Myeloma Group
VGPR – very good partial response

Conflict of interest: None declared.

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