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ISCHEMIA MODIFIED ALBUMIN LEVELS AND INCREASED OXIDATIVE STRESS IN PATIENTS WITH MULTIPLE MYELOMA

NIVOI ALBUMINA MODIFIKOVANOG ISHEMIJOM I POVIŠENI OKSIDANTNI STRES KOD PACIJENATA SA MULTIPLIM MIJELOMOM

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Summary

Background: Impaired oxidative/antioxidative balance plays an important role in the pathogenesis of many diseases, including cancer. The aim of this study was to evaluate the levels of the novel marker ischemia modified albumin (IMA) and albumin adjusted-IMA (Adj-IMA) in patients with multiple myeloma (MM) as well as its association with total antioxidant status (TAS), total oxidant status (TOS) and oxidative stress index (OSI).
Methods: Forty patients with MM (18 females, 22 males; mean age 67.55±8.39 years) and forty age/sex-matched healthy persons (19 females, 21 males; mean age 66.37± 6.76 years) were included in this study. Serum levels of IMA, TAS, TOS were analyzed and Adj-IMA and OSI was calculated.
Results: Serum IMA, TOS and OSI levels were significantly higher in patients with MM compared to controls ($p<0.001$ all parameters). There was no significant difference for serum albumin-adjusted IMA and TAS levels between groups ($p=0.83$ and $p=0.17$ respectively).
Conclusions: In this study, an impaired oxidative/antioxidant status in favor of oxidative stress was found in MM patients. This observation was not confirmed by Adj-IMA calculation. Further studies are needed to establish the relationship of IMA and oxidative stress parameters in multiple myeloma and their relationship to MM and other cancers.

Keywords: multiple myeloma, ischemia modified albumin, oxidative stress

Kratak sadržaj

Uvod: U patogenezi mnogih bolesti, poput raka, važnu ulogu igra pogoršan oksidantni/antioksidantni status. Cilj ove studije bio je da se odrede nivoi novog markera, albumina modifikovanog ishemijom (AMI) i AMI prilagođenog za albumin, kod pacijenata sa multiplim mijelomom (MM) kao i povezanost ovog markera sa ukupnim antioksidantnim statusom (UAS), ukupnim oksidantnim statusom (UOS) i indeksom oksidantnog stresa (IOS).
Metode: Studija je obuhvatila 40 pacijenata sa MM (18 žena, 22 muškarca; prosek godina 67,55±8,39) i 40 zdravih osoba odgovarajuće starosti i pola (19 žena, 21 muškarac; prosek godina 66,37±6,76). Serumski nivoi AMI, UAS i UOS su analizirani, dok je nivo IOS izračunat.
Rezultati: Nivoi AMI, UOS i IOS u serumu bili su značajno viši kod pacijenata sa MM nego u kontrolnoj grupi ($p<0,001$ za sve parametre). Između grupa nije otkrivena značajna razlika za serumski AMI prilagođen albuminu i nivoe UAS ($p=0,83$, odnosno $p=0,17$).
Zaključak: U ovoj studiji, kod pacijenata sa multiplim mijelomom utvrđen je izmenjen oksidantni/antioksidantni status u smislu povišenog oksidantnog stresa. Merenje AMI nije potvrdilo ovakav rezultat. Potrebne su dalje studije kako bi se ustanovio odnos između AMI i parametara oksidantnog stresa u MM i njihov odnos sa AMI i drugim vrstama raka.

Ključne reči: multipli mijelom, albumin modifikovan ishemijom, oksidantni stres

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Introduction

Multiple myeloma (MM) is a cancer of the plasma cells. It is the second most frequent malignancy of the blood in the USA after non-Hodgkin's lymphoma, accounting for 1% of neoplastic diseases and 13% of hematological malignancies. Clonal enlargement of the tumor cells results in the excessive generation of monoclonal immunoglobulin (Ig), which is a diagnostic property of this disease. Collection of monoclonal Ig light chains in the kidneys can lead to renal failure, which is usually shown in MM. A different feature of MM is the accumulation of malignant cells in the bone marrow, where they lead to osteolytic bone devastation and impaired hematopoiesis (1, 2). The etiology of multiple myeloma (MM) is unknown, but one of the suspects is the oxidative stress, as is the case in many other malignant diseases.

Albumin, the major plasma protein, has a number of cation and anion binding sites and effectively inhibits oxidation reactions in plasma. It acts both as a free radical scavenger and as a chelator of transition metals, making the protein a potent antioxidant. The free radical damage to the N terminal of albumin is the cause for the reduction in the binding affinity of albumin for metals (e.g. cobalt), which is the principle of some measurement methods for ischemia modified albumin (IMA) (3).

In recent years, studies have shown that IMA is a marker of myocardial ischemia, and it is accepted that IMA is an early marker to help in ruling out patients with acute coronary syndrome (4). However, the precise mechanism of IMA production is yet unknown (5). In one explanation: the body gets into an acidic state. Proteins that migrate along the ischemic area in the blood flow release divalent copper, and the copper ions (Cu^{+2}) are scavenged by albumin through tight binding to the N-terminus. The released divalent copper ions are reduced to monovalent copper ions in the presence of reducing substances such as ascorbic acid, and the monovalent copper ions produced by this mechanism react with oxygen to generate superoxide free radicals, which are converted to hydrogen peroxide (H_2O_2) by superoxide dismutase. Under normal conditions *in vivo*, hydrogen peroxide is converted to water and oxygen by catalase. However, in the presence of monovalent copper ions, H_2O_2 is converted to hydroxyl free radicals, through the Fenton reaction (3, 6, 7). These free radicals modify albumin, which is referred to as IMA, and release more divalent copper ions, thus generating more free radicals through the Fenton reaction. The resulting vicious cycle induces a sudden increase in IMA (3, 6, 7).

IMA levels are higher in many inflammatory and oxidative stress-associated diseases. There are various studies on IMA in patients with different states with ischemia of non-cardiac origin such as systemic sclerosis (8), peripheral vascular disease, skeletal muscle ischemia (9), glaucoma (10) and diabetes mellitus (11). Also, serum IMA levels are increased in patients with gastric (12), prostate (13), soft tissue cancer and neuroblastoma (14). There is no published report about serum concentrations of IMA in patients with MM. Due to the fact that cancer and oxidative stress belong to an associated event, and based on the fact that albumin may be modified in situations associated with oxidative stress, the aim of this study was to evaluate the levels of the novel marker IMA in patients with MM as well as its association with TAS, TOS and OSI.

Materials and Methods

Forty MM patients (18 females and 22 males; mean age 67.55±8.39 years) admitted to the Education and Research Hospital were prospectively included into the study. All the patients were newly diagnosed and in various stages of disease. The following paraproteins were assessed: IgG kappa in 21 patients, IgG lambda in 4 patients, IgA kappa in 6 patients, IgA lambda in 2 patients, IgM kappa in 5 patients and IgM lambda in 2 patients.

Forty healthy control subjects of corresponding gender and age (19 females and 21 males; mean age 66.37±6.76 years) were also enrolled for comparison. None of the participants in this study were using hypolipidemic agents or antioxidant drugs. This study did not include patients and controls with other systemic diseases such as hepatic failure, diabetes mellitus, coronary artery disease and active infection.

Blood samples were obtained after an overnight fast. Serum samples were then separated from cells by centrifugation at 3000 rpm for 10 min. Lipid parameters and other routine parameters were measured freshly. Remaining serum portions were stored at −80 °C and used to analyze IMA, TAS and TOS concentrations.

Analytical methods

Measurement of the ischemia modified albumin. Reduced cobalt to albumin-binding capacity (IMA level) was measured using the rapid and colorimetric method developed by Bar-Or et al. (15). Briefly, 200 mL of patient serum was transferred into glass tubes and 50 mL of 0.1% $CoCl_2 \times 6H_2O$ (Sigma-Aldrich Lot: S38901-248) was added. After gentle shaking, the mixture was incubated for 10 minutes to ensure sufficient cobalt albumin binding. Then, 50 mL of 1.5 mg/mL dithiothreitol (DTT) (Sigma-Aldrich Lot: D5545-1G) was added as a coloring agent. After two minutes, 1 mL of 0.9% NaCl was added to halt the binding between the cobalt and albumin. A blank was prepared for every specimen. At the DTT addition

step, 50 mL of distilled water was used instead of 50 mL of 1.5 mg/mL DTT to obtain a blank without DTT. The absorbances were recorded at 470 nm with a spectrophotometer (Shimadzu UV1201). Color formation in specimens with DTT was compared with color formation in the blank tubes, and the results were expressed as absorbance units (ABSUs). The formula suggested by Lippi et al. was used for calculation of albumin-adjusted IMA (AdJ-IMA) levels expressed as individual serum albumin concentration/median albumin concentration of the population × IMA value (16).

The interassay variability of IMA method in our laboratory was calculated from serum samples of 20 healthy subjects and 20 patients with acute coronary syndrome. The within-day coefficient of variation was 1.23% for healthy subjects (mean 0.365, standard deviation: 0.006) and for acute coronary syndrome 0.92% (mean 0.510, standard deviation: 0.006). All serum samples were analyzed within three days.

Measurement of serum total oxidant status. Serum TOS levels were analyzed by using a novel automated colorimetric measurement method developed by Erel (17). In this method, oxidants in the sample oxidize the ferrous ion–chelator complex to ferric ion which makes a colored complex with a chromogen in an acidic medium. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. The results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 Equiv./L).

Measurement of serum total antioxidant status. Serum TAS levels were analyzed by using a novel automated colorimetric measurement method developed by Erel (18). In this method, antioxidants in the sample reduce dark blue-green colored 2,2'-azinobis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) radical to colorless reduced ABTS form. The change of absorbance at 660 nm is related with total antioxidant level of the sample. This method determines the antioxidative effect of the sample against the potent free radical reactions initiated by the produced hydroxyl radical. The results are expressed as micromolar trolox equivalent per liter.

Oxidative Stress Index. The percentage ratio of TOS level to TAS level was suggested as the oxidative stress index (OSI) (19). For calculation, the resulting micromolar unit of TAS was changed to millimoles per liter, and the OSI value was calculated according to the following formula:

OSI (arbitrary unit) = TOS (micromolar hydrogen peroxide equivalent per liter)/TAS (micromolar trolox equivalent per liter).

Routine parameters. The levels of calcium (Ca), protein, albumin, creatinine, blood urea nitrogen (BUN) and uric acid were determined by using commercially available assay kits (Abbott) with an autoanalyzer (Architect ®c16000, Abbott Diagnostics).

The levels of hemoglobin (HMG) were determined by using a fully automated hematology analyzer (Sysmex ®xt-2000i, Roche Diagnostics).

Serum protein electrophoresis and immunofixation electrophoresis were detected using agarose gel via a Helena Biosciences Europe Electrophoresis instrument.

Statistical analysis

Statistical analyses were carried out using the statistical software version 11.5.1.0 (MedCalc, Mariakerke, Belgium). In normally distributed groups the results were presented with mean and SD, otherwise with medians and interquartile range (IQR). The significance of the differences between groups was determined by Student's unpaired t-test for normal distributions, and by the Mann-Whitney U test in abnormal distributions. Categorical variables were evaluated by using Fisher's exact test. Pearson correlation coefficient and Spearman correlation coefficient were used to test the strength of any associations between different variables. P value less than 0.05 was accepted as the significance level.

Results

When laboratory findings were compared, total protein, BUN, creatinine, uric acid levels were significantly higher among the MM patients [($p<0.0001$), ($p<0.0001$), ($p=0.0033$) and ($p=0.0003$), respectively]. The levels of hemoglobin and albumin were significantly lower in MM patients [($p<0.0001$) in both parameters]. Demographic data and laboratory findings for the MM and control patients are summarized in *Table I*.

Serum IMA, TOS and OSI levels were significantly higher in patients with MM compared to controls ($p<0.001$), whereas TAS levels were not statistically significant ($p=0.24$). There was no significant difference for serum Adj-IMA levels between groups ($p=0.32$) (*Table II*).

There were negative correlations between serum IMA and albumin levels (r: –0.43, $p=0.0001$) and positive correlations between IMA and TOS (r: 0.34, $p=0.002$), IMA and OSI (r: 0.35, $p=0.002$) levels. There was a positive correlation between Adj-IMA and albumin (r: 0.36, $p=0.0015$). There was no statistically significant correlation between Adj-IMA

Table I In patients with MM, albumin and hemoglobin levels were significantly lower, whereas total protein, BUN, creatinine, uric acid levels were significantly higher in comparison to the control group. The result values; for the normal distribution (mean±SD), for the abnormal distribution (median) (IQR).

Parameter	Patients (n=40)	Controls (n=40)	P
Age, mean±SD, years	67.5±8.4	66.4±6.8	0.47
Male, n (%)	22 (55%)	21 (52.5%)	0.99
Smoker, n (%)	12 (30%)	16 (40%)	0.48
Total protein, mean±SD, g/L	95±24	75±4	<0.0001
Albumin, mean±SD, g/L	34±8	44±2.5	<0.0001
Hemoglobin, mean±SD, g/L	91±23	137±12	<0.0001
Calcium, median (IQR), mmol/L	2.4 (2.30–2.42)	2.4 (2.27–2.35)	0.15
BUN, median (IQR), mmol/L	7.1 (5.7–8.9)	5 (4.3–5.7)	<0.0001
Creatinine, median (IQR), µmol/L	88.4 (71–107)	62 (53–63)	<0.0001
Uric acid, mean±SD, µmol/L	433±207	299±78	0.0003

Table II Serum IMA, Alb-Adj IMA, TAS, TOS and OSI levels of MM patients compared to the controls.

Parameter (mean±SD)	Patients (n=40)	Controls (n=40)	p
IMA (ABSU)	0.555±0.24	0.369±0.03	<0.0001
TAS (nmoL Troloks/Equiv./L)	2.9 (2.7–3.1)	2.8 (2.7–3)	0.24
TOS (µmoL H_2O_2 Equiv./L)	6.9 (4–13)	1.4 (1–1.6)	<0.0001
OSI	0.26 (0.1–0.4)	0.05 (0.04–0.06)	<0.0001
Adj-IMA (ABSU)	0.365±0.14	0.370±0.04	0.83

The result values; for the normal distribution (mean±SD), for the abnormal distribution (median) (IQR). ABSU: Absorbance Unit.

levels and TAS (r: 0.08, p=0.7), TOS (r: 0.03, p=0.9), OSI (r: 0.05, p=0.6) (*Table III*).

Hemoglobin, creatinine and calcium levels are important indicators for the prognosis of MM (16, 17). No statistically significant correlation was identified between hemoglobin, creatinine, calcium levels and IMA, Adj-IMA, TAS, TOS and OSI levels.

Table III Relationship of IMA and Adj-IMA with oxidative stress markers.

Parameter (n=80)	Albumin	TAS	TOS	OSI
IMA	r=–0.43 p=0.0001	r=0.13 p=0.2	r=0.34 p=0.002	r=0.35 p=0.002
Adj-IMA	r=0.36 p=0.0015	r=0.08 p=0.7	r=0.03 p=0.9	r=0.05 p=0.6

While there is a strong correlation between IMA and oxidative stress parameters, such a similar correlation can not be achieved with Adj-IMA.

Discussion

Our results showed oxidative stress markers (TOS, OSI) and IMA were increased in the patients with MM compared to healthy controls. Of concern, unlike IMA, adj-IMA calculation did not show a statistically significant between MM and healthy controls. We found a significant correlation between IMA and other oxidative markers. Adj-IMA does not seem to be correlated with oxidative stress parameters. Correlation of IMA with oxidative stress markers does not seem to be clinically significant for MM.

We analyzed adj-IMA levels using a formula suggested by Lippi et al. (16) according to individual and median population albumin levels. Serum IMA levels were significantly higher in patients with MM compared to controls, whereas serum albumin levels were significantly lower. There was no statistically significant difference for serum Alb-Adj IMA levels between groups. Our results are in close agreement with those previously reported. Studies evaluating the relationship between cancer and serum IMA levels are not too many. Fidan et al. (12) showed that serum IMA levels were increased in patients with gastric cancer. Mastella et al. (13) found increased serum IMA levels in patients with prostate cancer, but this increase was not statistically significant. Stachowicz-Stencel et al. (14) found that serum IMA levels were statistically higher in pediatric patients with neuroblastoma and soft tissue sarcomas. IMA levels were inversely related to serum albumin concentration (22–24) in these studies, which sufficiently disclosed the interrelation between IMA and albumin. The impact of serum albumin on IMA levels is still an important factor even within the normal range (28). Therefore, correction for albumin concentrations is essential in populations with wide variations in albumin levels. It has been demonstrated that each 10 g/L change in albumin within the physiologic range of albumin produces an opposite change of 2.6% in IMA levels, presenting a negative correlation (23). This proposes the exact

need to evaluate IMA values together with those of albumin to avoid possible false-positive or -negative values in individuals with hypo- or hyperalbuminemia. Our results clearly figure out the situation; as statistical analysis showed a strong correlation between oxidative stress markers and unadjusted IMA, but failed to repeat such a relation for adj-IMA.

Cancer patients suffer cachexia and malnutrition due to a variety of mechanisms involving the tumor, the host response, and anticancer therapies (26). Malnutrition and inflammation suppress albumin synthesis in the liver (27). The normal range of serum albumin for adults is between 35 and 50 g/L and a level <35 g/L is namely hypoalbuminemia (28, 29). The reverse correlation between body weight index and albumin synthesis in cancer patients supports the likelihood of a compensatory enhanced albumin synthesis in these metabolically influenced patients, which apparently fails in the further stages of disease, as malnutrition and inflammation override (30). Perhaps the most surprising is that suppression of albumin synthesis may be a defense mechanism against cancer. Under conditions of cellular stress, as in growing tumor tissue, albumin is taken up by cells as a source of amino acids and energy. The process was demonstrated with albumin covalently labelled with a fluorescent or a radiolabel dye (31). Fritzsche et al. (32) have shown albumin binding proteins to be expressed on various human tumor cell lines derived from solid tumors and on leukemic cells. Finally, serum albumin levels may change in cases of chronic inflammation and cancer, which should be a matter of consideration in IMA studies.

Sharma et al. (33) examined the levels of oxidative stress markers in 50 patients with MM and 50 healthy controls. These markers were SOD, GPX and catalase enzymatic activities in whole blood as well as the circulating levels of MDA, vitamin E and C. They determined that the average levels of SOD, GPX, catalase, vitamin E and C were lower in the patients with MM, while MDA levels were significantly higher. In our study, we found the difference of TOS and OSI between cancer patients and controls statistically significant. The conflict may be ascribed to different methodology used in case of Sharma et al. (33) although, very disputably, we find our result more reasonable, as the state of disease must be the failure of the organism to show a proportional response to the increase in oxidative stress. Measurement of TOS and OSI levels is extremely valuable as it informs about those oxidants not yet recognized or not easily measured. On the other hand, it is an unrefined, vague result, making it crucial to examine some subclasses of oxidants. However, no significant differences in TAS levels were identified when the two groups were compared. The reason for this increased TAS must be due to the increased uric acid levels in MM patients, which is an effective antioxidant.

In conclusion, we identified the presence of impaired oxidative balance in favor of oxidative stress in patients with MM. This observation was not confirmed by IMA measurement. However, our IMA vs. adj-IMA results must be considered to be a reminder that unadjusted IMA values might be quite deceptive, and may lead to inappropriate considerations. One major limitation of the study is the small number of samples. Obviously, larger studies are needed to establish the relationship of IMA and oxidative stress parameters in MM and relationship of IMA and other cancers.

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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