J. Elementol. 2009, 14(3): 563–571

MAGNESIUM CONCENTRATION IN PLASMA AND TISSUES OF PATIENTS UNDERGOING SURGERY FOR STOMACH AND LARGE INTESTINE CANCER

Monika Szewczyk, Kazimierz Pasternak, Andrzej Andrzejwski, Andrzej Dąbrowski, Grzegorz Wallner

Chair and Department of Medical Chemistry
2nd Chair and Department of General, Gastrointestinal and Oncological Surgery of the Alimentary Tract
Medical University of Lublin

Abstract

Digestive system neoplasms pose a serious health problem both in Poland and abroad. Neoplasms are frequently considered to be caused by impaired homeostasis in the human body. Development of neoplasms may be linked to disturbances in concentration of elements, including magnesium as a major intracellular cation.

The objective of this study was to evaluate the concentration of magnesium in plasma and tissue samples taken from patients suffering from neoplasms of the stomach or the large intestine.

The study involved 35 patients, including 20 affected by stomach cancer and 15 suffering from large intestine cancer. The patients were in the age rage of 36-77.

The material included blood samples taken from patients before and seven days after surgery, as well as samples of cancerous and healthy tissues. The colorimetric method with a Genesis spectrophotometer was used for determination of magnesium concentration.

A statistically significant difference was observed between plasma magnesium concentration in patients affected by stomach cancer and the normal range. Elevated values of magnesium concentration measured on the seventh day after the procedure as compared to the concentration before the procedure was noted, however, the difference was statistically insignificant. No significant differences were observed in magnesium concentration me-

Monika Szewczyk, Chair and Department of Medical Chemistry, Medical University of Lublin

asured before and after the procedure, or in comparison to the normal range in patients with large intestine cancer. Determination of tissue magnesium showed that magnesium concentration was higher in cancerous than in healthy tissue.

Obtained results demonstrate that magnesium homeostasis is impaired in patients, which may be important in the pathoghenesis of digestive system neoplasms.

Key words: magnesium, stomach cancer, large intestine cancer, hypomagnesemia, surgery.

STĘŻENIE MAGNEZU W OSOCZU I TKANKACH PACJENTÓW LECZONYCH OPERACYJNIE Z POWODU RAKA ŻOŁĄDKA I JELITA GRUBEGO

Abstrakt

Nowotwory przewodu pokarmowego stanowią istotny problem zdrowotny zarówno w Polsce, jak i na całym świecie. Przyczyny nowotworów często upatruje się w zaburzeniach homeostazy organizmu. Rozwój nowotworów może wiązać się z zaburzeniem stężenia pierwiastków, w tym również magnezu będącego najważniejszym kationem wewnątrzkomórkowym.

Celem pracy była ocena stężenia magnezu w osoczu i wycinkach tkanek nowotworowych chorych na raka żołądka i raka jelita grubego.

Badania wykonano u 35 pacjentów, w tym u 20 chorych na raka żołądka, oraz 15 chorych na raka jelita grubego. Badani byli w przedziale wiekowym od 36 do 77 lat.

Materiał do badań stanowiła krew chorych pobierana przed zabiegiem operacyjnym oraz w 7. dobie po zabiegu, a także wycinki tkanek zmienionych nowotworowo i zdrowych. Stężenie magnezu oznaczano metodą kolorymetryczną z użyciem spektrofotometru firmy Genesis.

U chorych na raka żołądka wykazano istotną statystycznie różnicę w stężeniu magnezu w osoczu w porównaniu z normą. Zaobserwowano również wyższe stężenie magnezu w 7. dobie po zabiegu w porównaniu ze stężeniem przed operacją, jednak różnica ta była nieistotna statystycznie. Natomiast w przypadku raka jelita grubego nie wykazano różnic istotnych statystycznie zarówno w stężeniu magnezu przed i po zabiegu, jak i przy porównaniu wyników stężeń magnezu z normą. Badając stężenie magnezu w tkankach, stwierdzono wyższe stężenie magnezu w tkance nowotworowej w porównaniu z tkanką zdrową.

Wyniki wskazują na istnienie zaburzeń homeostazy magnezu u chorych, co może mieć znaczenie w patogenezie nowotworów przewodu pokarmowego.

Słowa kluczowe: magnez, rak żołądka, rak jelita grubego, hipomagnezemia, leczenie operacyjne.

INTRODUCTION

Digestive system neoplasms are one of the chief causes of death from malignant tumors. The incidence rate of stomach and large intestine cancer in Poland is among the highest. Both stomach cancer and large intestine cancer are most frequently diagnosed in an advanced stage. Consequently, the efficacy of treatment and survival rate are low. Stomach cancer usually

affects people in the age range of 50-60, mostly female, while the incidence of large intestine cancer among males and females is comparable (Balcerska et al. 2000, Borch et al. 2000, Deheinzelin et al. 2000, Daradó et al. 2005).

Surgery is the basic and the most effective treatment of digestive system cancers. It is applied both in early and advanced stage carcinoma and involves radical removal of tumor. Hypomagnesemia frequently occurs in the post-surgery period, particularly following surgical treatment of stomach cancer (Hartgrink et al. 2002, Kim 2002, Machowska, Duda 2002, Popiela 2002, Borawska et al. 2005).

Advanced stage of digestive system neoplasms is usually accompanied by dysphagia and diarrhea, leading to emaciation, electrolyte disturbances and magnesium homeostasis disturbance. However, in early stages of cancerogenesis, patients have no symptoms and sings or the symptoms are non-specific (Tomatis 2000, Machowska, Duda 2002, Wolf et al. 2007).

Magnesium is a life essential intracellular macroelement, which is an activator of over 300 enzymes. It is a cell membrane stabilizer; it is essential to the synthesis of macroergic bonds and is active in protein synthesis as well as in nucleic acid metabolism. It plays an important role in the transportation of calcium, sodium and potassium ions. Magnesium deficiency in a period prior to a surgery may affect the patient's condition during and after the procedure. Even small changes in magnesium concentration induce changes in the cardiovascular system. Hypomagnesemia can have an inflammatory effect as it directly affects cells of the immune system, and by activating neuroendocrine mechanisms it produces an indirect effect. Low magnesium concentration causes more intensive activation of neutrophils and macrophages, increased production of inflammatory cytokines as well as excessive production of free radicals (Hartgrink et al. 2002, Hoenderop et al. 2005, Larsson et al. 2005, Starzyńska, Wasilewicz 2007).

The objective of this study was to determine magnesium concentration in plasma and cancerous tissue samples taken from patients suffering from stomach or large intestine cancer.

MATERIAL AND METHODS

The study was conducted at the 2nd Chair and Department of General, Gastrointestinal and Oncological Surgery of the Alimentary Tract Medical University of Lublin in the University Hospital SPSK No.1 in Lublin. The group of patients included 35 people who underwent surgical treatment of stomach cancer (20 subjects) or large intestine cancer (15 subjects). The subjects were in the age range of 36-77. Most of them, 63%, were men. Surgical removal of cancerous changes was the chosen treatment. About 85% of operations of stomach and large intestine cancer were planned. Most

of the patients were in hospital a few weeks during which they were diagnosed and medical treatment was applied. The patients did not have any symptoms and sings from the digestive system which could influence this study. No chemotherapy or radiotherapy preceded the surgical procedure. The subjects received no element supplementation. Study material included pre- and post-surgery plasma and tissue samples from the stomach and the large intestine.

The study was approved by the Bioethics Committee at the Medical University in Lublin. Approval no. KE – 0254/222/2007

Blood samples were taken before the procedure and on the seventh day after the procedure, and transferred to test tubes with the anticoagulant heparin.. Plasma was obtained by centrifuging whole blood samples at 3,500 rpm for 15 minutes.

Tissue material was obtained during surgery. Two samples were taken from each subject, one of cancerous tissue and the other one of possibly most distant healthy tissue. Tissue samples were bathed in 0.9% NaCl and stored at -40ºC until examination.

Tissue samples were defrozen and homogenized in Tris HCl (pH 7.4) buffer. Homogenates were centrifuged at 5,000 rpm for 15 minutes. Resulting supernatants were used for further examinations.

Magnesium concentration was determined with the colorimetric method using xylidyl blue which reacts with magnesium in alkaline solution to form a purple-coloured compound. The Cormay diagnostic kit Liquick Cor-Mg 60 was used. A single beam Genesis spectrophotometer with a wavelength at 520 nm was used to determine magnesium concentration.

The following statistical methods were used: Student's t-test, Cochran's C test and Cox test.

RESULTS AND DISCUSSION

The values of plasma magnesium concentration in subjects with stomach cancer ranged from 0.73 to 1.01 mmol l^{-1} before the surgery, and remained similar after the procedure, i.e. from 0.70 to 1.05 mmol l^{-1}. The values of plasma magnesium concentration measured before and seven days after the surgery were consistent with the normal range (Table 1). The mean magnesium concentration before the procedure was slightly lower than after the procedure.

The difference between the mean magnesium concentration in plasma of subjects suffering from stomach cancer before and after the surgery was statistically non-significant. However, there was a statistically significant difference between the values of magnesium concentration before and after the procedure versus the normal range.

Table 1

Plasma magnesium concentration in subjects

Specification	Plasma	No	From - to (mmol l^{-1})	Arithmetic mean	Median M	Standard deviation SD	Statistical significance IS pp*	Statistical significance ISn**
Stomach cancer	before	20	0.73 - 1.01	0.81	0.76	0.31	0.33	0.01
	7th day	20	0.70 - 1.05	0.94	0.86	0.24		0.01
Large intestine cancer	before	15	0.53 - 0.78	0.59	0.61	0.19	0.94	0.57
	7th day	15	0.48 - 0.62	0.51	0.48	0.06		0.67
Healthy	normal		0.60 - 1.1	0.85				

*level of statistical significance while comparing plasma Mg concentration in subjects before the surgery and on the 7th day after the surgery

**level of statistical significance while comparing plasma Mg concentration in subjects with the normal range

The values of plasma magnesium concentration in subjects with large intestine cancer were depressed (Table 1), ranging from 0.53 to 0.78 mmol l^{-1} before the surgery and from 0.48 to 0.62 after the surgery.

Similarly to stomach neoplasm, there was no statistical significance in the values of magnesium concentration before and after the surgery in subjects with neoplasm of the large intestine. Comparison of magnesium concentration before and after the procedure and the normal values did not demonstrate statistical significance.

In subjects with stomach cancer, the mean magnesium concentration reached 5.41 μg g^{-1} in healthy tissue and 6.18 μg g^{-1} in cancerous tissue. Analogously, in subjects with large intestine cancer, the mean concentration was 6.40 μg g^{-1} in healthy tissue and 6.77 μg g^{-1}. The study demonstrated that magnesium concentration was slightly higher in cancerous tissue (Table 2). The difference between magnesium concentration in cancerous and healthy tissue was statistically non-significant.

Table 2

Mean magnesium concentration in cancerous tissue

Specification	Tissue	No	From - to (μg g^{-1})	Arithmetic mean $\overline{x}$	Median M	Standard deviation SD	Statistical significance IS*
Stomach tissue	healthy	20	3.20 - 7.00	5.41	5.05	1.41	0.75
	cancerous	20	3.40 - 11.40	6.18	5.00	2.60	
Large intestine tissue	healthy	15	5.10 - 6.80	6.40	5.90	1.7	0.70
	cancerous	15	4.50 - 10.10	6.77	6.20	2.40	

*level of statistical significance by comparing Mg concentration in cancerous and healthy tissue

The etiopathogenesis of digestive system neoplasms is complex and not fully known yet. Neoplastic disease is often accompanied by disturbances in the concentration of macro- and microelements. Further disturbances may occur during treatment, especially when it involves surgery without accompanying element supplementation.

The body of a healthy adult contains approximately 24 g magnesium. More than 50% of the element is in the bones, ca 27% in the muscles and 19% in other soft tissues. Only 1% of the magnesium contained in the human body is found in blood, and its concentration in blood cells is almost three times as high as in serum. The latter ranges in a healthy person from 0.60 – 1.1 mmol l^{-1} (Głowania, Głowania 2000, Larsson et al. 2005, Lin et al. 2006).

Depressed magnesium concentration affects bone mineralization, the digestive system, the cardiovascular system, the reproductive organs, the im-

mune system as well as the muscular and the nervous system. Low concentration of magnesium in the human body may promote oncogenic activity of carcinogenic substances leading to an increase in the number of mutations responsible for neoplasm formation (DEHEINZELIN et al. 2000, OGRODNIK et al. 2004, DAI et al. 2007).

Numerous studies have been conducted on plasma magnesium concentration in subjects with neoplasms. There have been, however, fewer studies on its concentration in cancerous tissues.

This study has demonstrated the lack of significant differences between plasma magnesium concentration measured before the surgery and on the seventh day after the procedure. In stomach cancer, pre-surgery values were consistent with the normal range. On the seventh day after the procedure, magnesium concentration was slightly elevated but still consistent with normal values.

However, magnesium concentration in subjects suffering from large intestine cancer was below the normal range or took borderline values. The results obtained on the seventh day after the procedure showed that the concentration of magnesium was slightly lower in comparison to the pre-surgery values. This confirms the results of a study reported by MACHOWSKA and DUDA, who examined plasma in subjects with stomach or large intestine cancer. They found out that in subjects who were not given magnesium intravenously its concentration decreased and half of the patients developed postoperative hypomagnesemia persisting until the examination was completed, which happened on the fourth day (MACHOWSKA, DUDA 2002).

It has been found out that in subjects with digestive neoplasms the mean magnesium concentration was higher in cancerous than in healthy tissue. Similar results were obtained by NIEDZIELSKA et al. and BORAWSKA et al. in their studies on magnesium concentration in cancerous larynx tissue (NIEDZIELSKA et al. 2000, BORAWSKA et al. 2005). Increased magnesium concentration in cancerous tissue may be indicative of intensive metabolic processes in tumorous tissue.

Yaman et al. pointed out to the lack of significant differences between magnesium concentration in healthy and cancerous stomach tissue (YAMAN 2006, YAMAN et al. 2007, 2003). Olszewski et al. obtained similar results.

To sum up, disturbances in magnesium homeostasis, or even hypomagnesemia, occur in patients who undergo surgery for malignant tumor. Low magnesium concentration is found in plasma, while its concentration in cancerous tissues, where intensive metabolic process occur, is elevated.

Surgical procedure is an additional stress for the human body, therefore some researchers recommend magnesium supplementation in the pre- and post-surgery period. MACHOWSKA and DUDA (2002) noted beneficial influence of magnesium supply on the condition of patients after the procedure.

CONCLUSIONS

1. Large intestine neoplasms are accompanied by hypomagnesemia before and after a surgery.

2. Magnesium concentration is higher in cancerous than in healthy tissue.

3. Complete evaluation of interdependences between magnesium concentration and neoplasm formation requires further studies including more subjects.

REFERENCES

Balcerska A., Stachowicz-Stencel T., Łysiak-Szydłowska W. 2000. *Dynamika przebiegu choroby nowotworowej a stan bariery antyoksydacyjnej ustroju [Dynamics of the course of a neplastic disease and the antioxidative barrier of an organism].* Wiad. Lek., 3-4: 128-133. [in Polish]

Borawska M., Czyżewska E., Łazarczyk B., Socha K. 2005. *Wpływ nawyków żywieniowych na zawartość magnezu u ludzi z nowotworami krtani [Effect of nutritional habits on the concentration of magnesium in people suffering from laryngeal cancer].* Bromat. Chem. Toksykol., supl., 639-642. [in Polish]

Borch K., Jonsson B., Tarpila E. 2000. *Changing pattern of histological type, location, stage and outcome of surgical treatment of gastric carcinoma.* Br. J. Sur., 87: 618-626.

Dai Q., Shrubsole M., Ness R., Schlundt D., Cai Q., Smalley W., Li M., Shyr Y., Zheng W. 2007. *The relation of magnesium and calcium intakes and genetic polymorphism in the magnesium transporter to colonorectal neoplasia risk.* Am. J. Clin. Nutr., 86(3): 743--751.

Daradó A., Rzetecki T., Dziki A., Sapota A. 2005. *Poziomy biologiczne kadmu, cynku, miedzi i selenu u pacjentów z nowotworem jelita grubego [Biological levels of cadmium, copper and selenium in patients with large intestine cancer].* Bromat. Chem. Toksykol., 4(38): 371-376 [in Polish]

Deheinzelin D., Negri E., Tucci M., Salem M., Cruz V., Oliviera R., Nishimoto I., Hoelz C. 2000. *Hypomagnesemia in critically ill cancer patients: a prospective study of predictive factors.* Braz. J. Med. Res., 33(12): 1443-1448.

Głowania A., Głowania I. 2000. *Zastosowanie związków magnezu w praktyce lekarskiej [Use of magnesium compounds in therapeutic practice].* Med. Metabol., 1(4): 37-44. [in Polish]

Hartgrink H., Putter H., Klein Kranenbarg E. 2002. *Value of palliative resection in gastric cancer.* Br. J. Surg., 89: 1438-1443.

Hoenderop J., Bindels R. 2005. *Epithelial Ca^{2+} nad Mg^{2+} channels in health and disease.* J. Am. Soc. Nephrol., 16: 15-26.

Kim J. 2002. *Current status of surgical treatment of gastric cancer.* J. Surg. Oncol., 79: 79-80.

Larsson S., Bergkvist L., Wolk A. 2005. *Magnesium intake in relation to risk of colonorectal cancer in women.* JAMA, 293: 86-89.

Lin J., Cook N., Lee I., Manson J., Buring J., Zhang S. 2006. *Total magnesium intake and colonorectal cancer incidence in women.* Cancer Epidemiol. Biomarkers Prev., 15(10): 2006-2009.

MACHOWSKA B., DUDA K. 2002. *Hipomagnezemia u chorych operowanych z powodu nowotworów złośliwych żołądka oraz jelita grubego [Hypomagnsaemia in patients undergoing surgery for malignant neoplasmia of the stomach and large intestine].* Anestezjol. Intens. Terapia, 34: 172-177. [in Polish]

NIEDZIELSKA G., CARUK K., PASTERNAK K. 2000. *Pierwiastki śladowe w tkankach krtani objętych chorobą nowotworową [Trace elements in tissues of a larynx affected by neoplasmia].* Otolaryng. Pol., 4, supl. 31: 200-2002. [in Polish]

OLSZEWSKI J., LATUSIŃSKI J., KITA A. 2003. *Porównawcza ocena stężenia pierwiastków antyoksydacyjnych w surowicy krwi i bioptatach tkankowych u chorych z brodawczakiem lub rakiem krtani [Comparative evaluation of the concentration of antioxidative elements in blood serum and tissue bioptates in patients with papilloma and laryngeal neoplasma].* Otolaryngologia, 2(2): 90-93. [in Polish]

OGRODNIK W., KACZMAREK-BORAWSKA B., PASTERNAK K., GRĄDZIEL K. 2004. *Wpływ chemioterapii zawierającej doksorubicynę na stężenie magnezu i wapnia w osoczu krwi pacjentek chorych na raka piersi [Effect of chemotherapy containing doxorubicin on levels of magnesium and calcium in blood serum of patients with breast cancer].* J. Elementol., 9(3): 452-459. [in Polish]

POPIELA T., KULIG J., KOŁODZIEJCZYK P. SIERŻĘGA M. 2002. *Long-term results of surgery for early gastric cancer.* Br. J. Surg., 89: 1035-1042.

STARZYŃSKA T., WASILEWICZ M. 2007. *Chemoprewencja raka jelita grubego [Chemoprevention of large intestine cancer].* Pol. Merk. Lek., 23: 170-173. [in Polish]

TOMATIS L. 2000. *The identification of human carcinogens and primary prevention of cancer.* Mutat. Res., 462: 407-421.

WOLF F., MAIER J., NASULEWICZ A. 2007. *Magnesium and neoplasia: From carcinogenesis to tumor growth and progression or treatment.* Arch. Biochem. Biophys., 458: 24-32.

YAMAN M., KAYA G., YEKELER H. 2007. *Distribution of trace metal concentrations in paired cancerous and non-cancerous human stomach tissues.* World J. Gastroenterol., 13(4): 612-618.

YAMAN M. 2006. *Comprehensive compassion of trace metal concentrations in cancerous and non-cancerous human tissues.* Curr. Med. Chem., 13: 2513-2525.