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ORIGINAL PAPER

ASSESSMENT OF A THREAT OF HYPOMAGNESEMIA IN PATIENTS WITH CANCER, BASED ON PATIENTS' MEDICATION RECORD AND DIETARY QUESTIONNAIRE

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Abstract

Magnesium deficiency among oncological patients is a complex condition. Hypomagnesaemia is observed during anti-cancer chemotherapy and during treatment of certain co-existing disorders. Assessing the magnesium status is difficult, as serum levels have little correlation with the total body magnesium status. Thus, the aim of this study was to provide more recent data about possible causes of magnesium insufficiency among oncological patients with the focus on the health status, pharmacological treatment and intake of magnesium-rich food products. 380 oncological patients (304 reliable surveys) with concurrent chemotherapy, radiotherapy and surgery from the Clinical Department of Oncological Surgery, MSW Hospital, Olsztyn, Poland were reviewed retrospectively between January 2013 and April 2016. The mean magnesium dietary intake was 224 mg daily among women and 295 mg per day among men, which was found insufficient. Consumption of some food products rich in magnesium such as cacao, legumes, nuts and seeds was found to be scarce. Dietary supplementation of magnesium was also inadequate (3%). In addition, high daily consumption of coffee (67.1%) and strong tea (81.85%) was reported. Moreover, obesity (47.8%) together with gastrointestinal disorders such as diarrhoea and vomiting (52%) persisted, which may have further contributed to magnesium deficiency. Patient medication record has also revealed previous intake of some drugs that are implicated in the development of hypomagnesemia. Regular monitoring for enteritis and hypomagnesemia with timely intervention as well as inclusion of magnesium-rich food products in daily diet could help improve compliance, decrease the incidence of treatment interruptions and thereby help achieve the optimum treatment outcome.

Keywords: cancer, chemotherapy, cisplatin, electrolyte imbalance, hypomagnesemia, nutrition.

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INTRODUCTION

According to the WHO report from the year 2015, neoplastic diseases are a major cause of morbidity and mortality worldwide. Numerous reports indicate that patients with cancer can experience electrolyte imbalances, including hypomagnesaemia, hyponatremia, hypokalaemia, hyperkalaemia, hypophosphatemia, hypocalcaemia and hypercalcaemia (Lameire et al. 2010, Castiglioni, Maier 2011, Kaplinsky, Alon 2013, Namendys-Silva et al. 2014, Rosner, Dalkin 2014, Wang et al. 2015). In many cases this is due to common aetiology rather than cancer itself. Electrolyte imbalances, especially hypomagnesaemia and hypocalcaemia, are also associated with chemotherapy and with certain other anti-cancer drugs (Table 1).

Table 1

Anti-cancer drugs contributing to hypomagnesaemia

Medication	Group	Electrolyte imbalance	References
Cetuximab	Epidermal growth-factor (receptor) (EGFR) (R)-inhibitors	Hypomagnesaemia, hypokalaemia, hypocalcaemia	Wolf et al. (2009) Wang et al. (2015)
Ciclosporin	Immunosuppressant therapy	Hyperkalaemia, hypomagnesaemia	Saris et al. (2000)
Cisplatin	Platinum compound	Hyponatremia, hypokalaemia, hypocalcaemia, hypomagnesaemia	Saris et al. (2000) Wolf et al. (2009)
Hydroxycarbamide	Antineoplastic drug	Hypomagnesaemia	Altura et al. (2002)
Nilotinib	Antineoplastic drug	Hypomagnesaemia, hypophosphatemia, hypokalaemia, hyperkalaemia, hypocalcaemia, hyponatremia	Goldenberg (2008)
Panitumumab	Anti-epithelial growth--factor (receptor) monoclonal antibodies (anti-EGFR moabs)	Hypomagnesaemia, hypokalaemia, hypocalcaemia	Wang et al. (2015)
Pazopanib	Vascular-endothelial growth-factor (receptor) (VEGF)(R)-inhibitor	Hypomagnesaemia, hypophosphatemia	Schmidinger (2013)
Tacrolimus	Calcineurin inhibitor	Hyperkalaemia and hypokalaemia	Navaneethan et al. (2006)

Additionally, the combination of radiotherapy and chemotherapy produces significant toxicity to patients in conjunction with hypokalaemia, hypomagnesaemia and hypocalcaemia, which may further lead to the interruption

of cancer treatment and increased mortality (Harjani et al. 2014). Hypomagnesaemia can also contribute to the development of tumour-associated hypocalcaemia (D'Erasmo et al. 1991, Garrahy et al. 2016).

While hypermagnesaemia is relatively uncommon, hypomagnesaemia is a serious and life threatening condition among hospitalized patients, particularly with malignancy (Castiglioni, Maier 2011). Hypomagnesaemia is evident during treatment with certain anticancer drugs with the most significant being cisplatin and cetuximab. Additionally, other medications taken for co-existing diseases such as esomeprazole, digoxin, certain diuretics, antibiotics and antifungal drugs are able to potentiate the magnesium deficiency (Table 2). Moreover, the accompanying hypocalcaemia, diarrhoea and malnutrition can further aggravate the low magnesium concentration.

Magnesium homeostasis depends on the proper functioning of the gastrointestinal (GI) tract, bones and kidneys. In the human body, significant amounts of magnesium (approx. 50-60%) are mineralised in the bones, about 40-45% of this element is present in muscles and other soft tissues and about 1% is located in the extracellular fluid (Saris et al. 2000, Vormann 2003). Magnesium absorption takes place over the entire length of the colon (in the ileum and jejunum), thus the inflammation of the GI tract and other disorders of the GI may disturb magnesium absorption (Chandrasekaran et al. 2014). Increased kidney elimination may also influence magnesium status.

In addition, around one third of cancer deaths are due to five leading dietary and behavioural risks: lack of physical activity, high body mass index, low fresh fruit and vegetable consumption, tobacco and alcohol extensive use. Thus, proper diet with magnesium-rich food products is essential for obtaining maximum health benefits.

Large amounts of magnesium are found in cocoa, dark chocolate, cereal products (especially buckwheat), legumes (peas, beans), milk products (yogurt and kefir), whole and unrefined grains, seeds, nuts, almonds, chlorophyll (in green leafy vegetables, e.g. in spinach) and fresh fruits (Chandrasekaran et al. 2014). It is crucial to include magnesium-rich food products in daily diet of patients, as it is probable that magnesium deficiency may worsen the survival of oncological patients.

Of special interest is the magnesium status in a population of cancer patients, where magnesium deficiency is associated with inflammation and DNA mutations which may contribute to cancer development (Blaszczyk, Duda-Chodak 2013). In postmenopausal women alterations in the serum Ca/Mg ratio could lead to increased development of new and recurrent breast cancer (Sahmoun, Singh 2010). In addition, Abdelgawad et al. (2015) have shown that the Ca/Mg ratio was significantly higher in the breast cancer group suggesting magnesium deficiency. Total magnesium consumption was linked to a significantly lower risk of colorectal adenoma, particularly in those subjects with a low Ca/Mg intake (Dai et al. 2007). In addition, magnesium may play a significant role in control of diabetes, hypertension, athero-

Table 2

Electrolyte deficiency with induced hypomagnesaemia during pharmacological treatment with medications other than anti-cancer drugs

Medication	Group	Electrolyte imbalance	References
Amikacin, Gentamicin, Tobramycin	Aminoglycosides antibiotics	Hypomagnesaemia, hypocalcaemia, hypokalaemia	Saris et al. (2000)
Amphotericin B	Polyene antifungals	Hypokalaemia, hypomagnesaemia,	Atsmon, Dolev (2005)
Caspofungin, Micafungin	Echinocandin antifungals	Hypokalaemia, hypomagnesaemia, hypocalcaemia	
Digoxin*	Cardiac glycosides	Hypomagnesaemia	
Esomeprazole*	Proton pump inhibitors	Hypocalcaemia, hypomagnesaemia	Lin et al. (2015) Florentin, Elisaf (2012)
Foscarnet sodium	Antiviral drugs	Hypokalaemia, hypomagnesaemia, hypocalcaemia	Swaminathan (2000)
Furosemide* Hydrochlorothiazide	Loop diuretics, thiazide diuretics	Hypercalcaemia, hypokalaemia, hyponatremia, hypomagnesaemia	Saris et al. (2000)
Pamidronate disodium	Nitrogen-containing bisphosphonate	Hypophosphatemia, symptomatic hypocalcaemia, hypomagnesaemia, hyperkalaemia or hypokalaemia, hypernatremia	
Polystyrene sulfonate resins	Oral preparations for fluid and electrolyte imbalance	Hypomagnesaemia, hypokalaemia	Rajapakse (2009)
Zoledronic acid*	Bisphosphonate	Hypophosphatemia, hypomagnesaemia, hypokalaemia or hyperkalaemia, hypernatremia, hypocalcaemia	Epperla, Pathak (2015) Clark, Nystrom (2016)

* An asterisk indicates medication reported in patients medication history.

sclerosis, cardiac diseases, alcoholism, eclampsia and asthma (Wolf, Trapani 2012, Rubin 2014, Gröber et al. 2015). Magnesium deficiency may be the central precipitating event resulting in the kynurenine pathway dysfunction and accumulation of toxic quinolinic acid (Majewski et al. 2016).

The important role of magnesium makes its deficiency a potential health hazard. Thus, the aim of this study was to provide more recent data about possible causes of magnesium insufficiency among oncological patients with the focus on the intake of magnesium-rich food products, health status and pharmacological treatment.

MATERIALS AND METHODS

Subjects

The present study was based on a survey conducted among patients in the Oncology Polyclinic at the MSW Hospital in Olsztyn, Poland, hospitalised in one of the three wards: Radiotherapy, Chemotherapy and Oncological Surgery, from January 2013 to April 2016. The study included 380 patients, from which 304 (152 men and 152 women) reliable and complete surveys were selected for further evaluation. The patients' age ranged from 19 to 84 years, with a mean of 65±9 years in men and 54±8 years in women. Eighty -one patients (26.64%) were ≤ 50 years and 223 (73.36%) were > 50 years of age.

Questionnaire form

First, participants were asked to complete a general questionnaire comprising socio-demographic and anthropometric elements, including age, body mass, height and medical history. Body mass index was calculated by using height and body weight. The second part of the survey was constructed for this study exclusively and included: intake of coffee, tea and alcohol, use of vitamin and mineral supplements and consumption of some food products rich in magnesium, with the possible answers as to the frequency of intake: never, once a month, twice a month, three times a month, once a week, twice a week, three times a week, once a day, twice a day, three and more times a day. The third part included a 24-hour dietary recall by trained dieticians using an EPIC-SOFT computer program. During a recall, the patients needed to report the types and quantities of all foods and beverages consumed during the normal day at home. After 2-3 days, another 24-hour interview was carried out for comparison of subject variability in nutrient intake. The results were compared with the recommended daily allowance (RDA).

Data analyses

The results were calculated as a percentage of reliable surveyed patients. Data analyses were conducted using Microsoft Excel software. Data are expressed as a mean ± standard error of mean (SEM). Homogeneity of variance was tested for all data using the Levene's test. For parametric variables, Student's *t*-test was used to compare two experimental groups. The threshold level of significance was set at $P < 0.05$ using SPSS (version 24.00) software.

RESULTS

Subjects' characteristic

Obesity is associated with an increased risk of developing cancer of the colon and rectum, particularly among males. Overweight was diagnosed in 33.7% of oncological patients (40.5% in men and in 28.2% of women), I degree obesity in 11.4% (10.7% men and 11.7% women), whereas type II obesity was found in 2.7% of patients (2.3% and 3.1%, respectively). The correct weight was found in only 49.3% (43.5% men and 54% women) of respondents. Underweight occurred in 2.7% of patients (2.3% and 3.1%, respectively) – Figure 1.

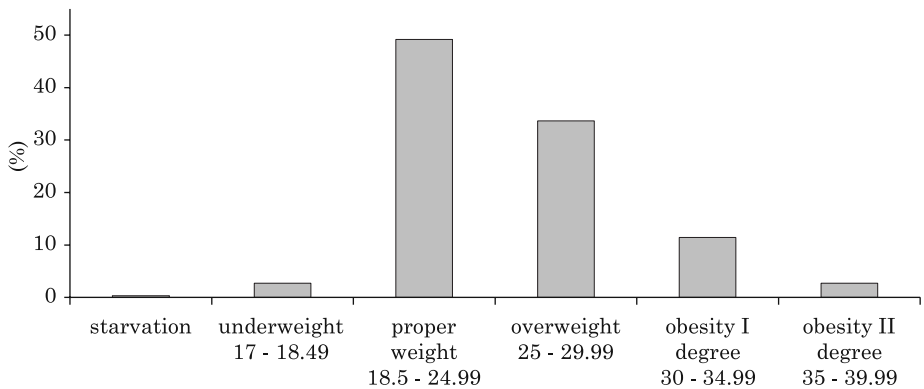


Fig. 1. BMI among oncological patients

Hypomagnesaemia is particularly evident during treatment with certain anticancer drugs, where the most commonly used drugs in our study were: cisplatin and cetuximab.

In the group of 304 respondents, 198 patients (62.1%) were suffering from additional diseases. Among the most common concomitant disorders in men were hypertension (56.3%), hypertension with diabetes (18.8%) and heart disease (5%). In the female group, the most frequent disorders were hypertension (46.5%), hypertension with diabetes (15.1%), diabetes (8.1%), hypothyroidism (7%), hypertension with hypothyroidism (5.8%) and depression (5.8%) – Figure 2.

Additionally, other medications taken for co-existing diseases are able to potentiate hypomagnesaemia. In our study, the most common drugs recorded as being taken in the patient medical history were esomeprazole, furosemide, digoxin and zoledronic acid.

The most frequently diagnosed sites of malignancy occurring in the analysed men's group were lung (29.5%), colorectal (17.0%), prostate (12.5%), liver (6.8%), larynx (6.8%), head (5.7%) and stomach (5.7%), whereas among women, the 7 most common sites diagnosed were: lung (20.0%), breast

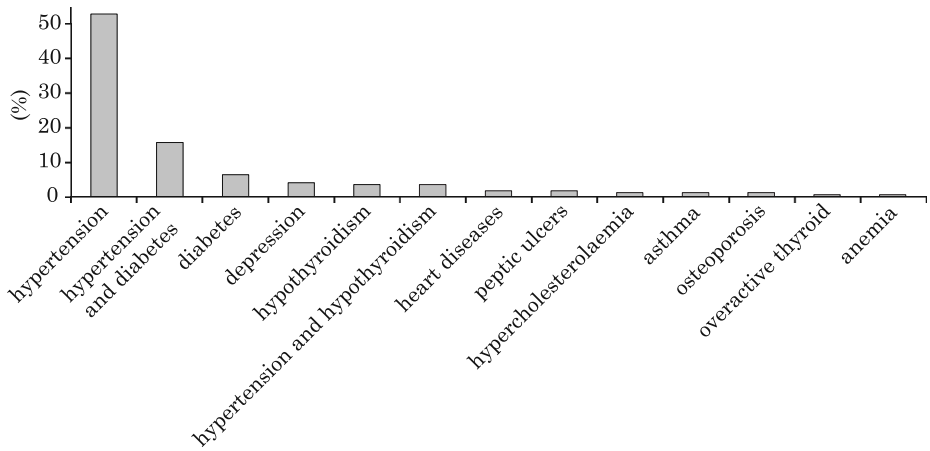


Fig. 2. Coexisting diseases among surveyed oncological patients. Depression (2.6%) was a third most commonly occurring disease after diabetes (44 patients – 14.5%) and hypertension (136 patients – 44.7%)

(20.0%), colorectal (16.0%), ovary and cervix (8.0%), liver (6.7%), uterus (5.3%) and skin (5.3%) – Figure 3.

Approximately 0.2% of lung cancers was diagnosed in patients between age 20 and 34 years; 1.5% between 35 and 44 years; 8.8% between 45 and 54 years; 20.9% between 55 and 64 years; 31.1% between 65 and 74 years; 29% between 75 and 84 years; and 8.3% at 85 years and older.

Contemporary methods of cancer treatment include chemotherapy (9%), radiotherapy (13.5%) and surgical interventions (24.5%). Also, a combination

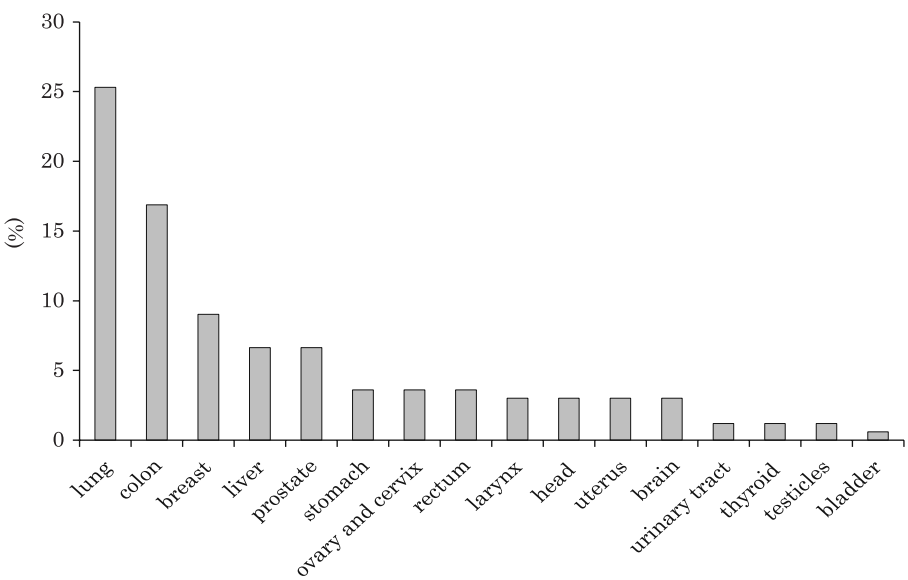


Fig. 3. Cancer prevalence among oncological patients diagnosed at the MSW hospital

of these methods is common in oncological patients, with the most prevalent approaches consisting of: chemotherapy and radiotherapy (16%), surgery with chemotherapy (11%) and a combination of all three methods, and the most frequent being surgery with chemotherapy and radiotherapy (11.5%) and chemotherapy, surgery and radiotherapy (7%) – Figure 4.

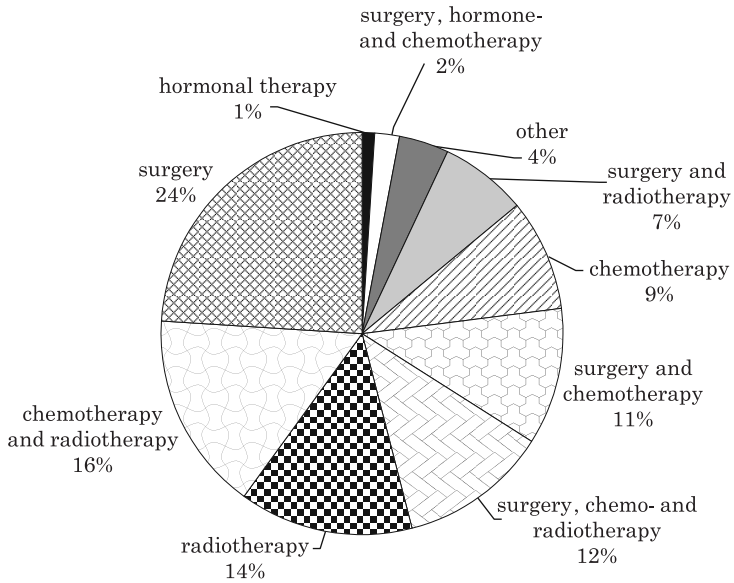


Fig. 4. Oncological treatment. High percentage of patients with chemotherapy (50%) and radiotherapy (49%) treatment may produce significant magnesium deficiency in patients

The percentage of all patients subjected to surgical intervention was 54%, radiotherapy 48% and chemotherapy 47.5%.

Improper functioning of the GI tract is the cause of poor absorption of nutrients and, if untreated, may lead to the malnutrition of the organism. Disturbances of the GI tract have been reported in 114 patients (37.5%). Among these the most common persistent problems were diarrhoea (21.8%), nausea (20.7%), diarrhoea with accompanying vomiting (16.1%), vomiting (13.8%), abdominal pain (13.8%) and constipation (9.2%). All GI tract disorders reported in the patient survey are presented in Figure 5.

Dietary, supplementation and magnesium-rich food products' intake

The mean magnesium intake was 259±8 mg daily and decreased with increasing age ($P < 0.01$). Men also had higher intakes of magnesium at 295±15 mg daily (RDA for magnesium in men 400-420 mg per day), whereas among women it was 224±12 mg daily (RDA 310–320 mg per day, $P < 0.01$).

In addition, the questionnaire surveys based on food intake revealed that the average consumption of magnesium-rich natural products was too infrequent to cover the recommended quantities. Whole seeds, unmilled grains, green leafy vegetables, legumes and nuts are the richest dietary sources of magnesium.

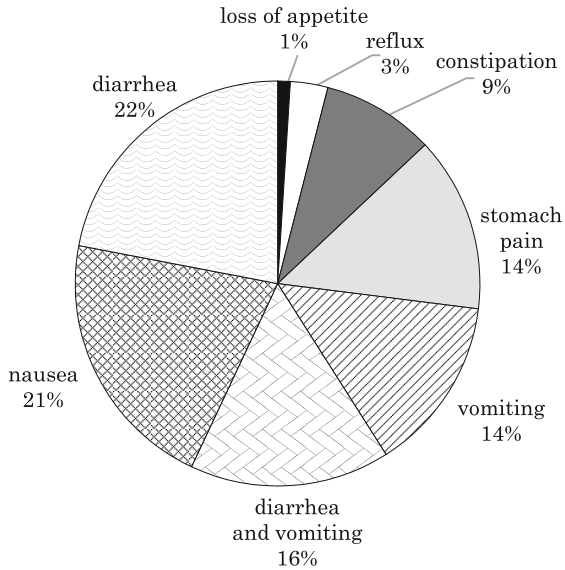


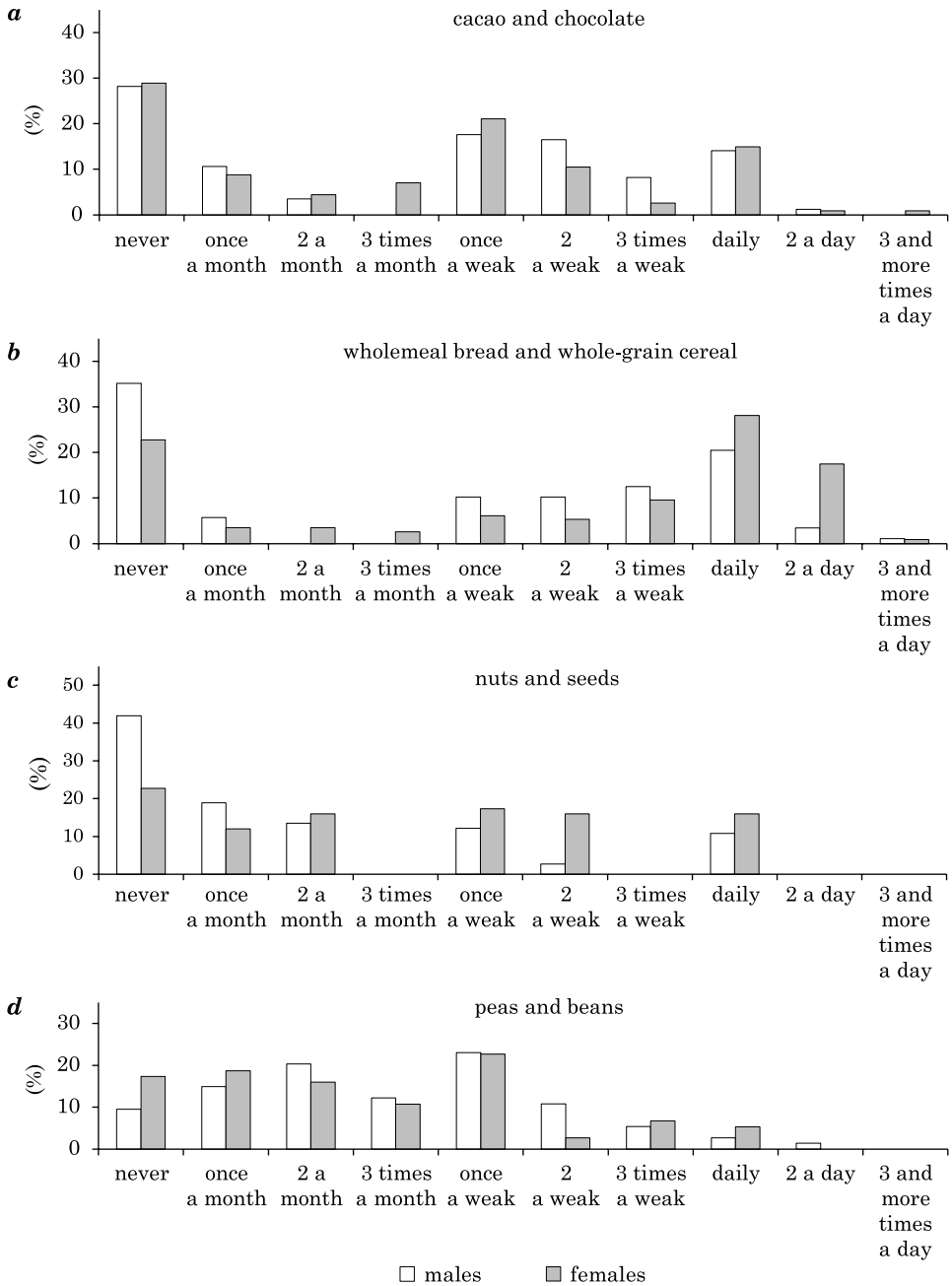
Fig. 5. The frequency of reported gastrointestinal tract disorders. 114 patients (37.5%) reported gastrointestinal side effects after drug administration with diarrhoea (38%) and vomiting (30%) occurring most frequently

In the group of oncological patients, 45.7% (42.3% men and 49.1% women) never or hardly ever consumed cacao and/or dark chocolate. Wholemeal bread and cereal products (especially buckwheat) were never or hardly ever eaten by 37.2% of oncological patients (42% of men and 32.4% women). Legumes (peas and beans) and nuts (with seeds) were rarely or never consumed by 59.8% (56.9% men and 62.7% women) and 62.5% (74.3% men and 50.7% women) of surveyed patients, respectively. Fresh fruit and vegetables were never or hardly ever consumed by 10.2% of patients (16.3% men and 4% women), whereas the cooked form was eaten by 20.2% (20.4% men and 19.9% women). Fresh green leafy vegetable were never or seldom consumed by 16.7% patients (28% men and 5.3% women). Figures 6*a*-*h* represent the consumption of magnesium-rich food products by both men and women.

Only 67 patients (22% of respondents) used supplementation with vitamins and minerals, and the most popular were vitamin C, vitamin D, calcium, magnesium and selenium (Figure 7).

Alcohol intake was reported by 50.2% of surveyed patients. 56.7% men and 45.1% women declared alcohol intake in the past. 32% of men and 21.5% of women stopped drinking due to diagnosed cancer. Men declared more frequent alcohol consumption as compared with the group of women (Figure 8*a*).

Excessive coffee and strong tea consumption (a few times a week and daily) was declared by 76.55% patients (82.5% men and 70.6% women) and 91.3% patients (89.3% men and 93.3% women), respectively (see Figure 8*b*, *c*).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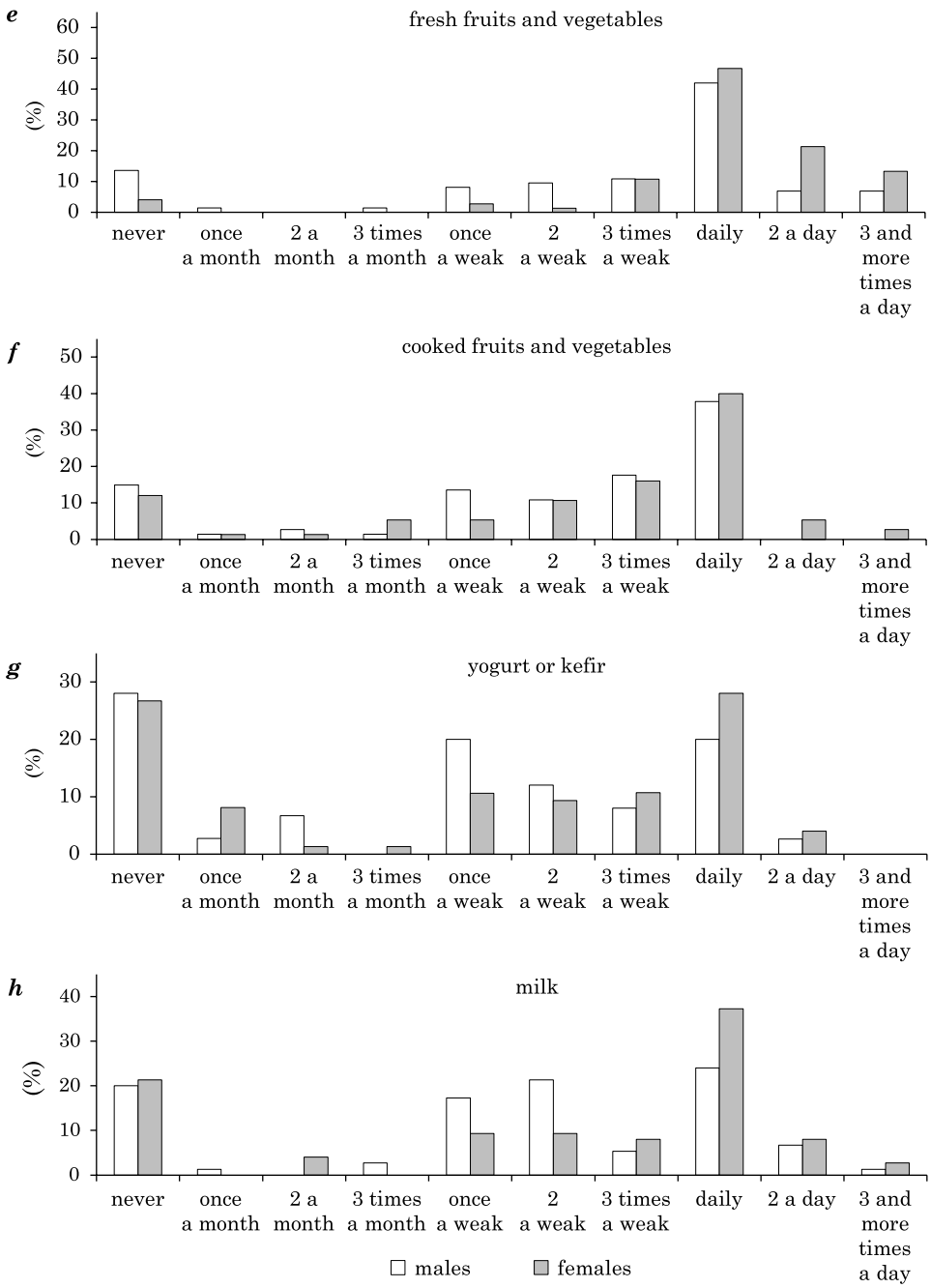

Fig. 6. Consumption of natural products rich in magnesium among surveyed oncological patients

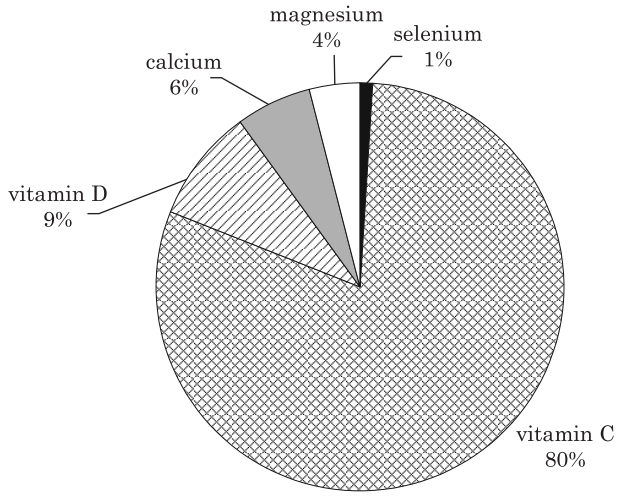

Fig. 7. Vitamin and mineral supplementation among oncological patients. Only 4% of those who used supplements (only 22% patients declared supplementation with vitamins and minerals) included magnesium supplementation in daily diet

DISCUSSION

Nearly 19 medications have been implicated as inducing hypomagnesaemia, based on clinical data. Certain drugs are able to induce 'significant' hypomagnesaemia (cisplatin, amphotericin B, ciclosporin), and routine magnesium monitoring is warranted, and preventive treatment of hypomagnesaemia should be started with or without overt clinical manifestations. In the second group of 'a potentially significant' category (amikacin, gentamicin, tobramycin, laxatives, pentamidine, tacrolimus and carboplatin), magnesium monitoring is of importance especially when one of the following occurs: clinical manifestations are apparent; persistent hypokalaemia, hypocalcaemia or alkalosis are present; other precipitating factors for hypomagnesaemia coexist; or treatment is with more than one potentially hypomagnesaemic drug. In the third group with diuretics, treatment should be started only if hypomagnesaemia is accompanied by symptoms or clinically significant relevant laboratory findings (Chandrasekaran et al. 2014). As there is a high percentage of patients treated with chemotherapy and radiotherapy, this may produce significant toxicity to patients in conjunction with electrolyte imbalance and hypomagnesaemia, which may further lead to interruption of cancer treatment and increased mortality.

The mean magnesium intake was highly below the recommendations. In such cases, supplements can be an important alternative source of magnesium. However, in our study, a large share of the participants did not consume supplements. Also consumption of some food products rich in magnesium was found to be scarce. Consumption of less than three servings of

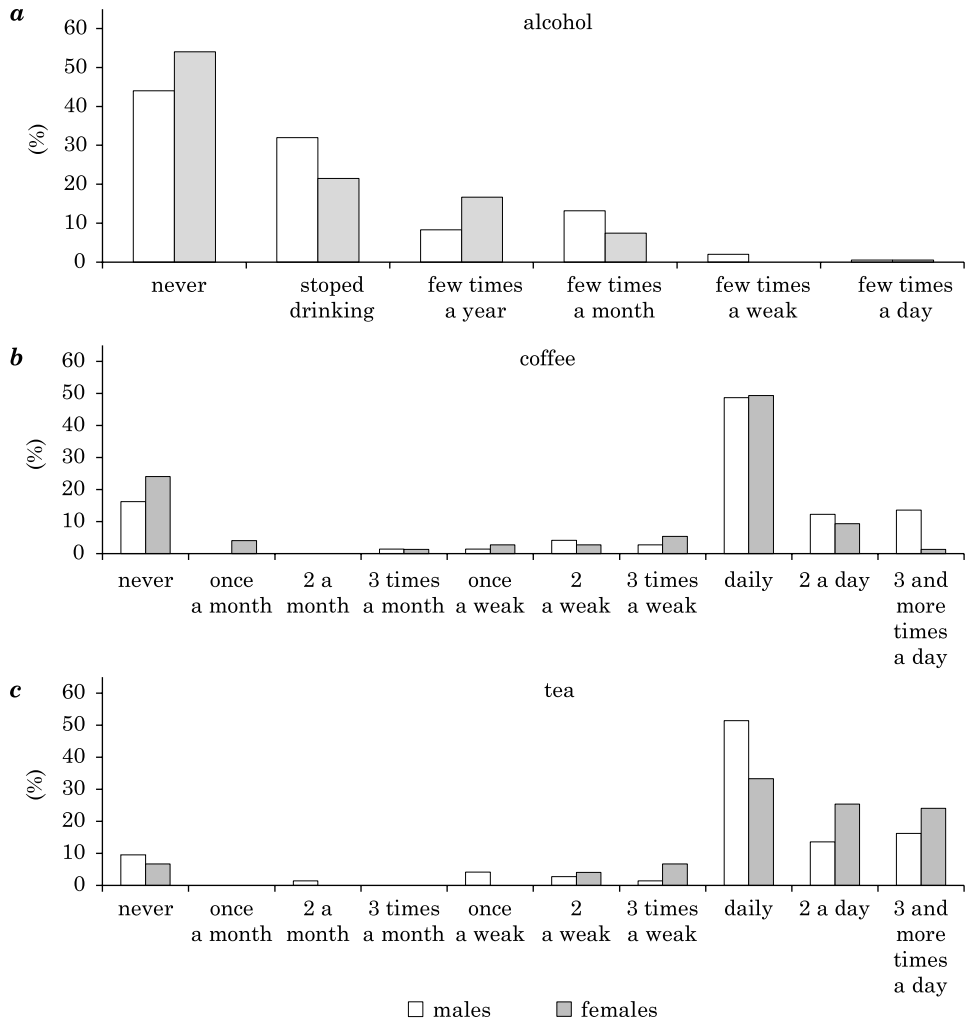

Fig. 8. Consumption of alcohol, coffee and strong tea among surveyed oncological patients

fresh fruit and vegetables per day has been reported in most of the patients.

A low magnesium status may also result from excessive coffee, strong tea or alcohol intake, together with malnutrition and obesity. High coffee and tea consumption has been reported by the surveyed patients,.

Magnesium deficiency is usually linked to disturbances in the intestinal absorption and/or increased renal magnesium excretion. Since magnesium is secreted in large amounts in the GI fluid, excessive losses during long-term diarrhoea and vomiting are the most common causes of hypomagnesaemia, which often induces secondary hypocalcaemia as well as hypokalaemia and hyponatraemia.

Moreover, impairment of magnesium absorption in patients suffering from GI cancer may also lead to magnesium insufficiency. Furthermore, people with coexisting disorders, such as type 2 diabetes, may have a lower magnesium concentration than people without this condition.

In conclusion, there is a major threat of hypomagnesemia in the population of oncological patients. Coexisting disorders, together with excessive intake of coffee and strong tea, may contribute to magnesium deficiency. Regular monitoring for enteritis and electrolyte disturbances, and timely restorative therapy can help improve compliance and decrease treatment interruptions, thereby achieving the optimum treatment outcome. The measurement of serum-magnesium concentrations is justified before and during prolonged treatment with a certain chemotherapy (cisplatin), especially when used with other drugs (such as digoxin) that cause hypomagnesaemia.

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