Blood plasma and saliva levels of magnesium and other bivalent cations in patients with parotid gland tumors

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Abstract. The plasma and saliva cations in parotid malignant tumors of stages II-III were studied in 31 patients before surgical therapy and in 27 control group volunteers. The magnesium (t-Mg), calcium (t-Ca), copper (t-Cu) and zinc (t-Zn) concentrations in plasma were determined, and t-Mg and t-Ca in saliva. Our results showed that salivary and plasma t-Mg concentrations were significantly higher in patients with parotid malignant tumors in comparison to control group (saliva: 0.25 ± 0.04 mmol/L versus 0.14 ± 0.03/L, p < 0.01; plasma: 1.05 ± 0.06 mmol/L versus 0.86 ± 0.05 mmol/L, p < 0.05). The t-Ca plasma concentrations were lower for patients with parotid malignant tumors by 20-22% in comparison to the control group (p < 0.05). Plasma and salivary t-Mg/t-Ca molar ratios are respectively 0.38 and 0.12 for control group, and respectively 0.61 and 0.31 for patients with parotid gland tumors. The t-Zn plasma concentration for patients with parotid malignant tumors (0.017 ± 0.010 mmol/L) was significantly lower (p < 0.05) in comparison to control group (0.024 ± 0.011 mmol/L). Plasma t-Cu/t-Zn molar ratio is respectively 0.68 for control group and 1.12 for patients with parotid gland tumors. The mechanism responsible for the increase of salivary magnesium as a consequence of the development of tumoral tissue needs to be clarified.

Key words: saliva, blood, parotid cancer, calcium, magnesium

Salivary gland tumors represent a heterogeneous group in oncological pathology. About 63% of salivary gland tumors occur in the parotid gland [1]. The major anatomopathological aspects of malignant parotid tumors are: mucoepidermoid carcinoma, adenocarcinoma, acinic cell carcinoma and adenoid cystic carcinoma [2]. Malignant tumors represent about 20-35% of all salivary gland tumors [3]. Malignant salivary gland tumors (MSGT) are uncommon. Age-standardized incidence rates are 0.5 and 0.3 per 100 000 in Quito, Ecuador; and 1.0 and 0.7 per 100 000 in the USA (SEER Program), for males and females, respectively [4]. Salivary gland neoplasms most commonly occur in the parotid glands (55-60%) followed by the submandibular and minor glands. Rapid growth or a sudden growth spurt characterizes the malignant salivary gland neoplasm (20 to 25%). The frequency of parotid gland malignant tumors is increasing continuously [5].
The oral cavity tissues are in permanent contact both with blood and saliva. Some modifications of the cation concentrations may be the consequence of pathological processes at the oro-maxilar area level. Magnesium and other divalent cations have important actions at the cellular level. Mg$^{2+}$ is required for a very wide range of cellular reactions, including all phosphoryl transfers, and its deprivation inhibits all components of the coordinate response. There is some evidence that plasmatic and cellular concentrations of magnesium and some other cations show variations during the development of malignant tumors. Deprivation of Mg$^{2+}$ in neoplastically transformed cultures normalizes their appearance and growth behavior and raises their abnormally low Ca$^{2+}$ concentration [6].

The aim of this study was to find changes of divalent cation concentrations in plasma and saliva during parotid carcinomatosis. The plasma concentrations of t-Mg, t-Ca, t-Cu and t-Zn were studied, simultaneously with the salivary concentrations of t-Mg and t-Ca.

**Patients and methods**

The study was approved by the Ethics Committee of St. Spiridon University Hospital in Iasi, Romania, and was conform to the rules for clinical trials. 58 patients were enrolled in this study. The group studied included 31 patients with 2nd or 3rd stage malignant tumors of the parotid glands, diagnosed in the Oro-Maxillo-Facial Surgery Clinic of St. Spiridon University Hospital (Iasi, Romania). The control group included 27 volunteers without malignant tumors or drug treatment recommendations.

Criteria for including patients were: 2nd or 3rd stage malignant tumors of the parotid glands, absence of bone metastasis (radiology examination), and the absence of administration of anti-neoplastic chemotherapy prior to the study. The parotid gland tumors were diagnosed by the following criteria: spontaneous pain not responding to treatment in an apparently benign tumor, characteristics of a malignant tumor (firm, nodular and usually fixed to adjacent tissue, poorly defined periphery, and appearance of paresis of facial nerve), modifications in sialography and other imagistic investigations. Anatomopathological examination (optical microscopy) of the tumor was performed for all cases. Criteria for exclusion were: presence of local tumor complications (necrosis, hemorrhages, inflammatory reactions), other malignant or benign tumors (wherever located), presence of oral mucosa acute or chronic inflammatory modifications, treatments with drugs containing magnesium or other cations, treatments with cardiac glycosides, diuretics, anti-hypertensive therapy, hormonal therapy, chronic diseases (liver cirrhosis, renal insufficiency, chronic ethanol consumption, malabsorption syndrome, endocrine diseases). Leukocyte count was normal for all included patients.

The following parameters were determined in the morning, 12 hours after the ingestion of food: t-Mg and t-Ca in saliva, respectively t-Mg, t-Ca, t-Cu and t-Zn in plasma. The blood samples (2 mL in tubes containing EDTA) were taken with a peripheral catheter. Saliva was collected by having the patient spit into a collection tube. Blood and saliva samples were centrifuged immediately to remove cellular elements or mucous. Supernatants were frozen at -80°C until metal concentrations were measured. The determinations of metal concentrations in plasma and saliva were performed by atomic absorption spectrophotometry (spectrophotometer type AAS1 Karl Zeiss, Jena, Germany) before the surgical interventions and/or radiotherapy and/or anti-neoplastic drug treatment. The T-Mg/t-Ca molar ratio in saliva and in plasma and T-Cu/t-Zn molar ratio in plasma were calculated. Student’s t-test was used for data analysis.

The study group included 17 men, 32 to 88 years old (59.9 ± 13.7 years) and 14 women 27 to 78 years old (55.4 ± 16.5 years). The control group included 19 men, 31 to 73 years old (58.8 ± 12.7 years) and 7 women 38 to 72 years old (55.6 ± 15.9 years).

The patients included in the study presented the following associated diseases: overweight (13 cases), blood hypertension (5 cases), osteoporosis (4 cases), neurosis (1 case), cholelithiasis (2 cases), incipient senile cataract (1 case), arthritic disease (1 case). Anatomopathological examination found the following types of malignant tumors: mucoepidermoid carcinoma (11 cases), adenoid cystic carcinoma (1 case), actinic cell carcinoma (4 cases), adenocarcinoma (7 cases), epithelial myoepithelial carcinoma (2 cases), squamous cell carcinoma (4 cases), and lymphomas (2 cases).

**Results**

The plasma and salivary t-Ca and t-Mg concentrations in patients with malignant tumors of the parotid glands and in the control group are presented in figure 1. Plasma and salivary t-Ca concentrations were significantly lower (p < 0.05) in patients with parotid malignant tumors (1.72 ± 0.13 mmol/L in
plasma and 0.81 ± 0.07 mmol/L in saliva) in comparison to the control group (2.28 ± 0.11 mmol/L in plasma and 1.21 ± 0.09 mmol/L in saliva). The t-Ca plasma concentrations were lower for the patients with parotid malignant tumors by 20-22% in comparison to the control group.

Plasma t-Mg concentrations were significantly higher (p < 0.05) in patients with parotid malignant tumors (1.05 ± 0.06 mmol/L) in comparison to the control group (0.86 ± 0.05 mmol/L). Salivary t-Mg concentrations were significantly higher (p < 0.01) in patients with parotid malignant tumors (0.25 ± 0.04 mmol/L) in comparison to the control group (0.14 ± 0.03 mmol/L).

Plasma t-Mg (0.86 mmol/L)/t-Ca (2.28 mmol/L) molar ratio was 0.38 for the control group, and the plasma t-Mg (1.05 mmol/L)/t-Ca (1.72 mmol/L) molar ratio was 0.61 for patients with parotid gland tumors. Saliva t-Mg (0.14 mmol/L)/t-Ca (1.21 mmol/L) molar ratio was 0.12 for control group and saliva t-Mg (0.25 mmol/L)/t-Ca (0.81 mmol/L) molar ratio was 0.31 for patients with parotid gland tumors.

**Figure 1.** Plasma and salivary concentrations of t-Ca and t-Mg in patients with parotid gland tumors and respective control subjects. *p < 0.05, **p < 0.01; significantly different from controls.

The t-Cu and t-Zn plasma concentrations in patients with parotid gland malignant tumors and in the control group are presented in figure 2. Plasma t-Cu concentrations were significantly higher (p < 0.05) in patients with parotid malignant tumors (0.019 ± 0.006 mmol/L) in comparison to the control group (0.016 ± 0.007 mmol/L). Plasma t-Zn concentrations were significantly lower (p < 0.01) in patients with parotid malignant tumors (0.017 ± 0.010 mmol/L) in comparison to the control group (0.024 ± 0.011 mmol/L). Plasma t-Cu (0.016 mmol/L)/t-Zn (0.024 mmol/L) molar ratio was 0.68 for the control group and plasma t-Cu (0.019 mmol/L)/t-Zn (0.017 mmol/L) molar ratio was 1.12 for patients with parotid gland tumors.

**Figure 2.** Plasma and salivary concentrations of t-Cu and t-Zn in patients with parotid gland tumors and respective control subjects. *p < 0.05; significantly different from controls.

**Discussion**

There are variations of the cation salivary concentrations in different physiological or pathological states. It has been shown that patients with periodontitis had decreased calcium in parotid saliva [7]. Significant differences in copper, zinc and iron concentrations in serum and saliva were observed.
between patients with various otorhinological disorders and the control groups [8]. The plasma copper/zinc ratio was found to be significantly higher in a lot of neoplasma [9, 10]. Advanced cancer is associated with disturbances in magnesium distribution and an increased magnesium level in the tumor. A high magnesium/calcium ratio level has been found in breast cancer [11]. Magnesium depletion appears more frequently in patients with some solid cancers [12]. A relatively higher magnesium/calcium ratio might induce tumor development by reducing apoptosis. On the other hand, it has been noticed that in the advanced stages of cancer evolution, t-Mg deficiency reduced tumor implantation and inhibited growth in spontaneous or experimentally induced tumors in rats [13].

Our data indicated higher plasma concentrations of t-Mg for patients with malignant tumors of the parotid glands compared to the control group, concomitant with a high salivary concentration of t-Mg for these patients. The increase of plasma and salivary concentrations of t-Mg is associated with a decrease of plasma and salivary t-Ca concentrations and an increase of the plasma and salivary t-Mg/t-Ca molar ratio. There is a concomitant decrease of t-Zn concentration and an increase of t-Cu concentration. We consider that higher t-Mg could be a factor which might stimulate the cellular proliferation and facilitate the development of malignant tumors. Some data sustain our opinion because t-Mg depletion causes cellular growth inhibition in certain cells [14]. The higher t-Mg (especially the cytosolic t-Mg) can reduce apoptosis and create conditions for cellular proliferation [15].

Our data are according to the results of Shpitzer et al. which demonstrated that salivary t-Mg in 25% patients with oral squamous cell carcinoma is 25% higher compared to the control group and with our previous results [16]. In our previous research, the increase of plasma concentrations was 22.3% compared to an increase of t-Mg salivary concentration which was 71.8% [17]. The molar ratio between t-Mg and t-Ca is different in the case of saliva, compared to plasma values. This is an argument against a relationship between the variation of t-Mg in saliva and plasma. It has to be noted that in the case of digitalis intoxication, the concentration of salivary t-Mg might be significantly increased compared to normal subjects, without an increase of plasma concentration of this cation [18].

Contrary to Garofalo et al. [19], who did not find significant modifications of t-Cu and t-Zn plasma concentrations in patients with epidermoid cancer of the head and neck, but according to our preliminary data [17, 20], the results demonstrated a significant decrease of t-Zn plasma concentrations in patients with non-metastatic parotid tumors. Our results are similar to data of Fong et al. who found low levels of Zn²⁺ associated with the development of 4-nitroquinoline 1-oxide induced oral tumors in mice [21]. In our previous study [20] the plasma level of t-Zn was lower in patients with oro-maxillary cancer.

There are data on the role of zinc in the reduction or prevention of oncogenesis in different tissues. Killilea et al. demonstrated that zinc deficiency reduces paclitaxel efficacy in prostatic cancer cells [22]. Bitar et al. consider that zinc might be an adjuvant therapy for juvenile onset recurrent respiratory papillomatosis [23]. Zinc content is lower in secondary liver cancer compared to livers from healthy patients [24]. A decrease of hepatic zinc and an increase in the value of the Cu/Zn ratio was found in the hepatocarcinogenesis in rats initiated by diethylnitrosamine [25]. Similar results were obtained for breast cancer [26]. Buntzel et al. demonstrated a decrease of plasma zinc in patients with cancer in the head and neck [27]. It could be considered that zinc has an important role in the prevention of the development of malignant tumors. Dany et al. demonstrated that zinc administration had a beneficial effect against experimentally chemically induced colon carcinogenesis [28].

Interestingly, in the present work we show a parallel increase of salivary t-Mg and of the plasma molar ratio of t-Cu/t-Zn in the case of parotid gland tumors.

Conclusion

The t-Cu/t-Zn and t-Mg/t-Ca plasma molar ratios were significantly higher in patients with parotid gland malignant tumors of stages II-III (without metastasis) compared to the control group. The salivary t-Mg concentration and the t-Mg/t-Ca salivary molar ratio were higher in parotid gland neoplasms. Changes in the plasma molar ratios of some cations and the concomitant statistically significant increase of plasma t-Mg and decrease of plasma t-Zn might be a consequence of the evolution of tumors. We consider that these changes in plasma and saliva ions are deeply involved in the development of malignant parotid tumors. The mechanism responsible for the increase of salivary magnesium as a consequence of the development of tumoral tissue needs to be clarified.
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References


