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Serum levels of selected adipocytokines in benign and malignant parotid gland tumor patients

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ABSTRACT

Objectives: The aim of this study was to evaluate serum levels of adiponectin, leptin, visfatin and IL-6 in patients with pleomorphic adenoma, Warthin's tumor and acinic cell carcinoma of the parotid gland.
Materials and methods: Venous blood samples were collected from 30 patients with pleomorphic adenoma, 21 patients with Warthin's tumor and 8 patients with acinic cell carcinoma. Serum adiponectin, leptin, visfatin, IL-6 and CRP concentrations were determined.
Results: Our results revealed significantly lower adiponectin serum levels in patients with malignant tumors compared to benign tumor individuals. Moreover, in benign cases the level was significantly higher compared to controls. Furthermore, serum leptin concentrations of benign tumor patients were higher compared to controls. Those differences, however, were observed only in males. The serum visfatin level was elevated in all tumor subjects compared to healthy individuals, whereas the serum IL-6 concentration was similar.
Conclusions: We anticipate that adiponectin may play a potential protective role in salivary gland tumors. Also leptin and visfatin seem to play an important role in salivary gland tumor pathology, although in males and females leptin may act or be regulated in a different manner. The influence of visfatin on salivary gland tumors is probably independent of IL-6 production.

1. Introduction

It is well known that the adipose tissue is not a simple energy depot, but plays an important role as an autocrine and paracrine organ. Adipocytokines (also called adipokines) released from the adipose tissue consist of over twenty molecules acting both locally and peripherally regulating a large number of physiological processes [1]. Moreover, altered homeostasis of the adipose tissue observed e.g. in obesity leads to many pathological conditions such as the metabolic syndrome with its co-morbidities. Interestingly, also in non-obese subjects, adipocytokines seems to be related with some pathologies, e.g. digestive tract malignancies [2].

Adiponectin, released from the adipose tissue, is a cytokine exerting anti-inflammatory properties, mainly known for its role in the pathology of insulin resistance and diabetes [3]. Moreover, its direct and indirect impact on tumori- and cancerogenesis was proposed [4]. Similarly, leptin was proposed to influence the pathophysiology of malignances [5,6]. Under physiological conditions, leptin regulates appetite and energy expenditure [7]. Visfatin, also known as PBEF (Pre-B cell colony-enhancing factor) and Nampt (nicotinamide phosphoribosyltransferase), is an adipocytokine exerting pleomorphic effects (insulin-mimic effects, pro-inflammatory and NAD – nicotinamide adenine dinucleotide – regulatory actions) and is also linked with a number of cancers [8–10].

In last several years there is an increasing evidence for connection of obesity, the adipose tissue and finally adipocytokines with some oncological diseases. For some time adipocytokines are the target of investigation in tumor pathology [8] and some of them are promising targets in the treatment of selected malignancie [11]. Among others, adiponectin, leptin and visfatin were presented to have the impact on those pathologies [8] although their influence on salivary gland tumors are still under investigation. Only some reports considering adipocytokines in salivary glands physiology and pathology can be found in the present literature [12–16], and just a few considers salivary gland tumors [7,14,17]. Adiponectin and leptin are produced and locally secreted in salivary glands including parotid gland [5,14,18] moreover visfatin was also presented in salivary gland cells [19] Taking under consideration the role of adipocytokines in pathology and treatment of

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some malignancies, their presence in salivary glands and their still not clearly understood impact on salivary gland tumors, we decided to examine serum concentrations of adiponectin, leptin and visfatin in benign and malignant parotid gland tumor patients.

The incidence of total salivary gland tumors is difficult to determine, but it may range annually to even 13 cases per 100,000 population [20]. It means that considering the region of Silesia (about 4.5 mln population) [21] there might be diagnosed even more than 550 cases of salivary gland tumors every year. Fortunately, most of those tumors are benign (~84%) and involve the largest salivary gland i.e. the parotid gland. Among benign tumors pleomorphic adenoma (PA) and Warthin's tumor (WT) are the most frequent pathologies (~65% and ~29%, respectively) [20].

Considering an increased number of patients with salivary gland tumors reporting not only to our Department, but also to other clinics around Poland and Europe, we believe that further understanding in that matter is of increasing importance. Therefore, we examined serum levels of adiponectin, leptin and visfatin in normal-weight patients with the most common tumors of the parotid gland i.e. PA and WT, and also malignant acinic cell carcinoma (ACC).

2. Material and methods

2.1. Patients

We examined 112 normal-weight patients with parotid gland tumor who were admitted to the Department of Laryngology and Oncological Laryngology in Zabrze, Medical University of Silesia in Katowice, Poland. Patients with previous oncological treatment, diabetes mellitus, obesity or other metabolic disorders were excluded from the study. Moreover, the results of individuals with fasting plasma glucose above 5.56 mmol/L were not accepted into the experiment. Therefore, 30 patients with pleomorphic adenoma (PA group), 21 patients with Warthin's tumor (WT group) and 8 patients with acinic cell carcinoma (ACC) were enrolled in the study. The control group consisted of 30 healthy gender-, BMI- and age-matched individuals, admitted to our Department for nasal septum surgery with no pansinusitis or other laryngological impairments (Table 1).

Venous blood samples (5 ml) were taken from patients after obtaining informed consent, after 6 h-fasting period during standard procedures of admission to the Department. The samples were immediately centrifuged, frozen and stored in −80 °C until the final examination.

The type of parotid gland tumor surgery in the examined groups was determined according to the suggestions of the European Salivary Gland Society [22]. In the ACC group 1 patient underwent superficial parotidectomy (Par I-II) as a consequence of a benign tumor diagnosed by fine-needle biopsy.

Table 1
Demographic characteristics of the examined groups.

Examined groups	Control (n = 30)	PA (n = 30)	WT (n = 21)	ACC (n = 8)
Age (years ± SD)	55.5 ± 9.4	54.1 ± 12.4	58.1 ± 6.8	59.9 ± 8.2
Female/Male	20/10	20/10	12/9	5/3
BMI (kg/m^2 ± SD)	22.9 ± 2.8	23.5 ± 2.2	23.2 ± 1.8	23.8 ± 0.9
Surgery type				
ECD	NA	3	1	0
Par I or II		5	12	0
Par I–II		18	3	1
Par I–III		4	5	0
Par I–IV		0	0	7
Mean tumor size (mm) (min–max)	NA	26 (11–56)	24 (8–42)	28 (18–30)
Tumor side Right/ Left	NA	21/9	14/7	3/5

Abbreviations: PA – pleomorphic adenoma group; WT – Warthin's tumor group; ACC – acinic cell carcinoma group; BMI – body mass index; ECD – extra-capsular dissection; Par – parotidectomy; SD – standard deviation; NA – non-applicable.

2.2. Biochemical analysis

Serum adiponectin, leptin, visfatin and IL-6 concentrations were determined using ELISA methods (R&D, USA, Elx 800 device – BIO-TEK Instruments, USA). The concentrations of CRP were determined using standard methods (Cobas 600 analyzer, Roche, USA).

2.3. Statistical analysis

The statistical analysis was performed using Statistica 12 (StatSoft) and Excel (Office, Microsoft) software. The normality of the distribution of the results was tested using the Shapiro-Wilk test. The parametric t-Student test for was used as detection test for the significance of differences between groups. The correlations were estimated by the Pearson method. The level of significance was established at $p < 0.05$.

Due to the fact that the ACC group had a relatively small number of subjects, the results in this group were presented only in total, without gender distribution.

The experimental protocol was approved by the local ethical committee of the Medical University of Silesia in Katowice No KNW/022/KB1/106/16.

3. Results

In all of our subjects CRP concentration was below 5.0 mg/L. Moreover, CRP levels in PA, WT and ACC patients were similar to controls (1.76 ± 0.88 mg/L, 1.75 ± 1.21 mg/L and 2.16 ± 0.98 mg/L *vs* 2.09 ± 1.35 mg/L, respectively).

3.1. Serum adiponectin concentration

In our results, the serum adiponectin level in controls differed between genders. It was significantly higher in female compared to male subjects (6.15 ± 1.82 μg/mL *vs* 8.19 ± 1.81 μg/mL; $p = 0.01$). Interestingly, the mean adiponectin concentration was significantly higher in benign tumor patients compared to controls in both genders in PA (23.72 ± 6.83 μg/mL; $p = 0.0004$ in males; 24.12 ± 9.46 μg/mL; $p = 0.0002$ in females) and WT groups (16.11 ± 7.41 μg/mL; $p = 0.0008$ in males; 18.92 ± 8.15 μg/mL; $p = 0.0003$ in females). The results of PA and WT groups were statistically similar and did not depend on the gender of patients in those groups (Fig. 1). Considering

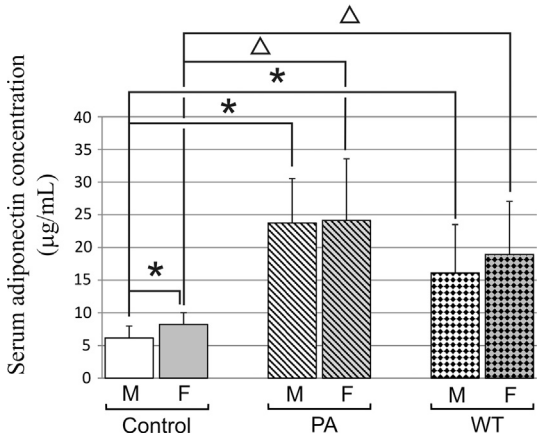

Fig. 1. Serum adiponectin concentrations (μg/mL) with gender distribution (M – males, F – females) in PA – pleomorphic adenoma group, WT – Warthin's tumor group and Control. *$p < 0.05$ *vs* male Control group; Δ$p < 0.05$ *vs* female Control group. Data are presented as mean ± SD.