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The Relationship between IL-6 and Nutritional Status in Patients with Gastrointestinal Tumors

Valéria Jósa[1], Valentin Brodszky[2], Zsombor Zrubka[2], Attila Zaránd[3], Tünde Mezei[4], Zsuzsanna Szilasi[5], Adrienne Fehér[6], Iván Igaz[7], Krisztián Somlai[8], Keresztély Merkel[9] and Zsolt Baranyai[3]*

[1]Department of Otorhinolaryngology and Head and Neck Surgery, Jahn Ferenc Hospital, Budapest
[2]Department of Health Economics, Corvinus University of Budapest, Hungary
[3]1st. Department of Surgery, Semmelweis University, Hungary
[4]Department of Urology, Jahn Ferenc Hospital, Budapest, Hungary
[5]Department of Otorhinolaryngology and Head and Neck Surgery, HDF Medical Centre, Budapest, Hungary
[6]Department of Laboratory Medicine, Semmelweis University, Hungary
[7]Department of Gastroenterology, Szent Imre Hospital, Hungary
[8]Department of Surgery, Szent Margit Hospital, Hungary
[9]Department of Surgery, Szent Imre Hospital, Budapest, Hungary

Abstract

Introduction: IL-6 is an essential factor in inflammatory processes; its level has been found to be elevated in a variety of gastrointestinal tumors. Nearly 30% of IL-6 circulating in the blood is produced by adipose tissue; however, there are no clear data on whether its level changes in obese patients.

Material and method: We studied 127 patients with gastrointestinal tumors of different stages. IL-6 levels, white blood cell count (WBC), and hemoglobin (Hgb) concentration were determined in preoperative blood samples. BMI was determined with a calibrated calculator, before surgery. During the statistical analysis of the data, correlation was calculated using Spearman, Wilcoxon, and Pearson correlation coefficients.

Results: In patients with various gastrointestinal tumors, the level of circulating IL-6 was unrelated to BMI. This result was not influenced by hemoglobin concentration, or by white blood cell count.

Conclusion: In gastrointestinal tumors, IL-6 production by adipose tissue is negligible as compared with cytokine expression by the tumor and its environment.

Keywords: BMI; Nutritional status; IL-6; Gastrointestinal tumor

Introduction

Neoplastic disease and obesity are among the most alarming public health problems of developed countries [1,2]. According to the literature, obesity and the increase of the body-mass index (BMI) are associated with an enhanced risk of esophageal, colorectal, pancreatic, and gallbladder neoplasms, as well as of postmenopausal breast tumors and endometrial cancer [3-8]. In overweight (BMI 25 to 29 kg/m^2) and in obese (BMI ≥30 kg/m^2) patients, the incidence of these tumors increases from 3% to 10% [9]. The exact underlying pathomechanism is unknown. Elevated serum IL-6 levels were observed in patients with various gastrointestinal tumors [10-12]. In the neoplastic microenvironment, the primary sources of IL-6 include tumor cells, tumor-associated macrophages (TAM), CD4+ T cells, myeloid-derived suppressor cells (MDSC), and fibroblasts [13-16]. IL-6 has a regulatory role in nearly every process of tumorigenesis: it inhibits apoptosis [17,18], as well as facilitates survival [19,20], proliferation [21,22], and angiogenesis [23]. Further, it enhances invasiveness and metastasis formation [16,24], and stimulates the metabolism of tumor cells [25,26]. Adipose tissue (abdominal fat, in the first place) produces nearly 30% of IL-6 present in the systemic circulation [27]. Our study intended to clarify whether excess bodyweight has any influence on IL-6 serum level in patients with gastrointestinal neoplasms.

Material and Method

Between 2014 and 2106, we studied 245 patients undergoing surgery for gastrointestinal (esophageal, hepatic, gallbladder, gastric, pancreatic, large bowel, rectal, and small intestinal) tumors at the 1st Department of Surgery of Semmelweis University (Budapest, Hungary). The exclusion criteria were as follows: age under 18 years, inflammatory disorders (including pneumonia, wound infection, cholecystitis, peripheral cannula sepsis, endocarditis, urinary tract infection, Crohn's disease, ulcerative colitis), thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism, myocardial infarction), steroid therapy, anemia (hemoglobin level <120 g/L), and artificial nutrition. Demographical and clinical data were accumulated. Preoperative blood samples were obtained closest to the time of surgery, for the measurement of IL-6 levels at the Institute for Laboratory Medicine of Semmelweis University, using an ADVIA 2120 hematology analyzer. The same blood sample was used for the measurement of white blood cell count, and of hemoglobin concentration. BMI values were determined preoperatively, with a calibrated calculator.

Statistical analysis

During the statistical analysis of study data, correlation was calculated using Spearman, Wilcoxon, and Pearson correlation

***Corresponding author:** Zsolt Baranyai, 1st Department of Surgery, Semmelweis University Budapest, Hungary, Tel: +3630/4500-388; E-mail: barazso@gmail.com

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coefficients. Means were compared with the paired t-test. Statistical analyses were performed at a 95% confidence level.

Results

Based on the foregoing, 118 patients altogether had been excluded in the first place because of the presence of various inflammatory processes and thus, 127 patients were evaluated. Our study cohort was heterogeneous with regard to the types and stages of the variety of gastrointestinal tumors (Table 1). A relatively large proportion of these patients had a colorectal or a pancreatic tumor.

Among the study parameters, the extreme elevation of IL-6 levels was observed only in patients with gallbladder tumors. However, mean white blood cell count was also above the upper limit of the normal range; moreover, it is not possible to draw any meaningful conclusion from only two cases. The proportions of lean/normal-weight and of overweight/obese patients studied were similar. We did not find significant differences among the individual BMI categories, regarding neither the study parameters, nor the BMI categories by body-weight (Table 2).

The univariate analysis showed a significant correlation of IL-6 level with white blood cell count and hemoglobin level, but not between BMI and IL-6 level. The multivariate analysis confirmed a similar relationship: neither hemoglobin concentration, nor WBC influence the correlation between serum IL-6 levels and BMI (Table 3).

Discussion

Oncologists, researchers, and epidemiologists have demonstrated a relationship between excess body weight and the risk of malignancy. Hyperglycemia of 10- to 20-year duration is associated with 44-per-cent increase, whereas preexisting, elevated, abnormal fasting blood glucose level is accompanied by a 57-per-cent increase of cancer risk [28]. Moreover, the malignant tumors occurring in obese patients have a worse prognosis [29]. The pathological background of the relationship between these two disorders has not yet been fully clarified. However, several hypotheses exist as to the possible tumorigenic mechanisms active in adipose tissue. Fat tissue produces estrogen, this leads to elevated circulating hormone level – and hence, hormone-sensitive tumor types begin to proliferate. Elevated insulin level also affects cellular growth and has an important role in the metabolism of tumors.

The production of IL-6 is regulated in the first place by variations in the gene expression of various transcription factors, such as NF-kB, CCAAT/enhancer-binding protein A, activator protein 1 (a major transcriptional regulator) – although post-transcriptional changes have also been identified [30,31]. In the systemic circulation, IL-6 level approaches 1 pg/ml [32,33]; however, its elevation can be observed in many conditions, including acute hyperglycemia [34], the consumption of food with high fat content [35], normal menstruation cycles [36], and physical activity [37], as well as during/after surgical interventions [38]. Furthermore, a dramatic elevation of IL-6 level has been observed in sepsis [39]. Physical activity is an important stimulus for the enhanced gene expression and production of IL-6. In particular, most of the circulating IL-6 is released from contracting muscles, and this may lead a hundredfold elevation of physiological IL-6 level in the systemic circulation [37,40]. During physical activity, IL-6 produced by exercising muscles serves as an energy-sensor, which triggers AMP-activated protein kinases, increases glucose uptake, and enhances lipolysis [37]. IL-6 sensitizes the myotubules for insulin. Furthermore, low glycogen level in muscle tissue enhances the production of IL-6 and its release from myocytes [41]. Abundant data suggest that IL-6 facilitates the development of insulin resistance [42]. The production of a substance by exercising muscle that increases insulin resistance may appear paradoxical. However, it is postulated that insulin resistance induced by IL-6 serves as a defense mechanism, which protects the organism against hypoglycemia induced by muscle activity [43].

Tumor type	Number of cases	Sex (males/females)	Age (mean)	Tumor stage				IL-6 (pg/ml) (mean)	BMI (kg/m²) (mean)	WBC (G/L) (mean)	Hgb (g/L) (mean)
				1	2	3	4				
Esophageal	10	10/0	59.2	0	3	4	3	6.855	24.49	7.325	132.3
Hepatic*	8	4/4	64.1	2	2	3	1	5.0488	27.69	5.6371	129
Gastric	25	19/6	66.7	3	4	4	14	11.7684	24.96	7.4062	120.71
Pancreatic	30	17/13	65.5	3	10	11	6	16.4007	25.90	9.02	121.36
Colorectal	28	15/13	67.5	2	8	10	8	10.9564	25.98	7.5717	117.48
Rectal	22	18/4	58.2	3	7	7	5	11.4055	25.74	8.2824	131.86
Gallbladder	2	0/2	61.3	0	0	0	2	100.575	23.74	11.53	118
Small intestinal	2	0/2	57	0	0	0	2	2.06	26.72	6.14	131

*Barcelona criteria: Stage 1=A, Stage 2=B, Stage 3=C, Stage 4=D.

Table 1: Clinical properties and laboratory parameters.

Variables	BMI (kg/m²)			P (F) value
	Lean/normal (<25)	Overweight (25-30)	Obese (≥30)	
Number of cases	56	52	19	—
IL-6 (pg/ml) mean (SD)	17.0 (29.8)	9.6 (25.3)	11.3 (19.5)	0.337
WBC (G/L) mean (SD)	8.1 (3.0)	7.7 (3.2)	7.8 (3.5)	0.869
Hgb (g/L) mean (SD)	122.2 (18.9)	124.0 (21.1)	129.0 (14.5)	0.485

Table 2: Means ± standard deviation by individual BMI categories.

Variables	Univariate analysis		Multivariate analysis	
	Pearson's correlation coefficient	P-value	Regression coefficient (95% CI)	P-value
BMI	-0.062	0.488	-0.10 (-1.23-1.03)	0.861
WBC	0.379	<0.001	3.17 (1.63-4.72)	<0.001
Hgb	-0.252	0.007	-0.31 (-0.56--0.06)	0.016

Table 3: The relationship of IL-6 level with body mass, white blood cell count, and hemoglobin concentration.

In the microenvironment of the tumor, IL-6 supports tumorigenesis by direct action on the modulation of the intrinsic and extrinsic activity of tumor cells [44]. Basically, tumor cells produce IL-6 to promote their own survival and dissemination, whereas they do not depend on the paracrine release of IL-6 produced by stromal cells. In tumor cells, the possible stimulatory effect of IL-6 is mediated by the activation of a number of signaling pathways. IL-6 stimulates the proliferation and survival of tumor cells by activating the Ras/Raf/MEK/MAPK, PI3K/AKT, and JAK/STAT pathways through the phosphorylation of gp130 tyrosine residues [22,45]. The majority of the genes involved in the regulation of cell survival and proliferation, including Bcl-2, Bcl-xL, Mcl-1, Fas, cyclin D1, cyclin E1, and p21 are direct targets of STAT-3 along with pro-proliferation transcription factors (such as c-Myc, c-Jun, and c-FOS). In tumor cells, STAT-3 activation is mediated by the autocrine production and the paracrine secretion of IL-6 by stromal and immigrant inflammatory cells [13-16,46,47]. IL-6 has been found to mediate multiple hemopoietic effects by shifting stem cells from the G_0 to the G_1 stage of the cell cycle, and thereby to induce their proliferation and to enhance their responsiveness to additional hematopoietic factors. The latter include IL-3, IL-4, G-CSF, M-CSF, and GM-CSF [48]. The autocrine production of IL-6 by non-stem cells activates the JAK1/STAT-3 signaling pathway, which plays an important role in the transformation of non-stem cells to stem cell-like cells by up-regulating Oct-4 (a stem cell marker) [49]. Thus, IL-6 not only induces tumor cell proliferation, but also maintains their population, and this induces tumor recurrence.

Conclusion

According to our findings, the level of circulating IL-6 was not dependent on BMI in patients with various gastrointestinal tumors. This suggests that in these cases, IL-6 production by adipose tissue is negligible as compared with cytokine expression by the tumor and is environment. Similar to chronic disorders and to long-standing inflammation, tumor-associated anemia greatly elevates IL-6 level [50,51]. Refractory anemia can develop as a consequence of pre-existing protein-energy loss [52]. A dramatic increase of IL-6 level has been found in sepsis [39]. In view of the foregoing, we also checked the hemoglobin concentrations and the white blood cell counts of our patients; however, neither of these parameters influenced the correlation between BMI and IL-6 [53].

Our method for measuring BMI has its limitations. BMI informs about the patient's height-related body mass; however, it tells nothing the type of the tissue accrual underlying the latter [54]. Therefore, while it is a reliable indicator of obesity at population level, body mass index is of limited value when it is determined in individuals. The measurement of circulating leptin or adiponectin levels, or the assessment of body fat percentage (e.g. by computed tomography) would be much more appropriate for evaluating obesity [55]. Notwithstanding this, we believe that our findings are of potential interest, and motivate us for further research in this subject.

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