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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: Valéria Jósa

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/m²) and in obese (BMI 30 kg/m²) 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.

Materials and methods

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

coe cients. Means were compared with the paired t-test. Statistical analyses were performed at a 95% con dence level.

Based on the foregoing, 118 patients altogether had been excluded in the rst place because of the presence of various in ammatory 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. e proportions of lean/normal-weight and of overweight/obese patients studied were similar. We did not nd signi cant di erences among the individual BMI categories, regarding neither the study parameters, nor the BMI categories by body-weight (Table 2).

e univariate analysis showed a signi cant correlation of IL-6 level with white blood cell count and hemoglobin level, but not between BMI and IL-6 level. e multivariate analysis con rmed a similar relationship: neither hemoglobin concentration, nor WBC in uence the correlation between serum IL-6 levels and BMI (Table 3).

D

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]. e pathological background of the relationship inc-9.6

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.

C

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 its 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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