Serum insulin levels in patients with colorectal cancer

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Abstract: Introduction. Insulin regulates metabolic processes and is an important growth factor, which is able to stimulate cell proliferation and transformation and to inhibit apoptosis. **Objectives.** The aim of the study was to analyze the fasting serum insulin level in patients with colorectal cancer in relation to the clinical stage of the disease, patients' overweight and obesity, and the localization of a tumor (in the colon and rectum). **Patients and methods.** Seventy patients with colorectal cancer, including 41 men and 29 women (at an average age of 65 years) were enrolled into the study. Patients with diabetes, other forms of cancer, or used hormones were excluded from the study. Medical records of the patients was evaluated. Glucose and insulin levels in blood serum were analyzed. All the patients were divided into groups according to the body mass index (BMI), the clinical stage of the disease (including TNM) and tumor localization. **Results.** Ten patients (14.29%) were obese, 31 patients (44.29%) were overweight, and 29 patients had normal weight (41.43%). The average BMI was 25.98 ±5.38 kg/m^2. The mean glucose serum level was 5.49 ±1.0 mmol/l and the mean insulin serum level was 18.93 ±14.67 μIU/ml. There were no significant differences in glucose and insulin levels in relation to the stage of the disease, tumor localization and BMI. **Conclusions.** Overweight and obesity were observed in most of the colorectal cancer patients. No statistical associations were observed between serum insulin levels and tumor localization.

Key words: body mass index, colorectal cancer, insulin, glucose

INTRODUCTION

Several epidemiological studies showed an increased risk of many types of cancer in type 2 diabetic or obese patients [1-4]. On the basis of a meta-analysis of 15 studies performed in the years 1966–2005 with over 2.5 million participants, Larsson et al. [5] showed a relationship between type 2 diabetes and an increased risk of colorectal cancer, both in men and women. Other investigatos highlighted the coexistence of type 1 diabetes and colorectal cancer [3]. Importance of hyperglycemia and hyperinsulinemia in cancerogenesis and the coexistence of these disorders in patients with colorectal cancer were stressed in a number of studies [6-8].

Uterine, prostate and breast cancer are also related to metabolic disorders [9-12]. Among the environmental factors associated with an increased risk of colorectal cancer is a high-calorie diet with excessive fats and fiber deficiency. Fat stimulates the secretion of bile acids, which are transformed by intestinal bacteria into secondary and tertiary acids. These, in turn, may cause mutation in intestinal epithelial cells. On the other hand, fiber deficiency impairs the intestinal passage, which increases the exposition of intestinal cells to cancerogens present in the intestinal contents [6]. Insulin and insulin-like growth factor-1 (IGF1) are factors for diet-dependent cancers [3,13-15]. Insulin can be characterized by intracellular, pleiotropic action, associated on the one hand with metabolic effects – the metabolism of glucose, proteins and lipids, and on the other hand with growth-promoting effects, the proliferation of cells, and their influence on apoptosis and the cellular cycle [16]. The growth factor effect, which promotes tumor development, is reported during high levels of this hormone. The mitogenic influence of insulin can be reported as a result of binding with the insulin-like growth factor-1 receptor (IGF1R) – the autophosphorylation of this receptor is of key importance in the generation of growth and proliferation-related signals [3,14,17].

The aim of this study was to analyze serum insulin levels in patients with adenocarcinoma of the colon, depending on the ad-

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Received: January 8, 2008. **Accepted in final form:** April 18, 2008.
Conflict of interest: none declared.
Pol Arch Med Wewn 2008; 118 (5): 273-279
Translated by Professional Language Services SIGILLUM Ltd., Kraków

vancement of the clinical stage, a degree to which the patient is overweight or obese, and the localization of tumor.

PATIENTS AND METHODS

The study was performed among 70 patients (41 men and 29 women) with established diagnosis of adenocarcinoma of the colon. The patient average age was 65 years. Coexistent diseases were considered during the patient selection. Patients suffering from diabetes, other cancers and using hormonal medications were excluded from the research group. Tumors were localized in 39 patients (55.71%) in the colon and the sigmoid colon, in 31 patients (44.29%) in the rectum. All patients underwent surgery to cure or provide palliative treatment. A clinical pathological grade (IIV) was established on the basis of the surgical procedure protocol, histopathological examination and additional tests, in concordance with the 4th TNM classification from 1986 accepted by the TNM Committee of the International Union against Cancer (UICC) (published in English in 1987). The 1st clinical grade was recognized in 14 patients (20%), the 2nd grade in 18 patients (25.71%), the 3rd grade in 22 patients (31.43%) and the 4th grade in 15 patients (21.43%). In 1 patient (1.43%), the clinical pathological grade could not be established on the basis of available medical records. The most numerous group was formed by patients with diagnoses of adenocarcinoma or ulcerative and mucous adenocarcinoma, and who displayed grade G2 histopathological malignancy (Tab. 1). Subsequent antitumor treatment was planned depending on the clinical grade of the disease, tumor location, valid rules of the oncological management, age, general condition, coexistent diseases and consent to the proposed treatment. Patients were treated or followed-up in the Oncological Clinic/Specialistic Hospital Department No 4 in Bytom, or the Chair and Clinical Department of Internal Medicine of the Silesian Medical University in Bytom.

Selected data from the medical documentation of patients were analyzed. Qualitative variables, i.e. sex, the clinical grade of colon adenocarcinoma, weight category and occurrence of cardiovascular diseases were analyzed. The qualitative variables analyzed included the patient's age, body mass index (BMI – kg/m^2), fasting glucose (mmol/l) and fasting insulin level (μlU/ml) values in blood serum. Glucose level was routinely examined upon the patient's qualification for surgery and established from the average of 3 measurements. Insulin level assay was additionally performed at the time of routine tests (from one injection from the antecubital vein), after the surgical treatment and before qualification for supplementary (randomized trials, controlled trials or randomized controlled trials), follow-up or palliative treatment. The patients gave an informed consent to the study and additional measurements were made. The study was approved by the Bioethical Committee of the Silesian Medical University (L.dz. NN-6501-79/06) from 24.05.2006.

Insulin level assay

The insulin serum level was assayed with the ELISA method, with the use of BioSource INS-EASIA Kit set (catalogue number KAP1251) by the BioSource Europe S.A. (Belgium) according to the manufacturer's instructions. Absorption was taken with the ELISA reader (PowerVave XS, Biotek, USA) at a wavelength of 450 nm. The substance level value was read from the curve for insulin level patterns and expressed in μlU/ml. Measurements were made in duplicates. The variability percentage between samples varied from 3.1 to 9.6%. The average method sensitivity was 0.15 μlU/ml.

Selected data for epidemiological evaluation were transferred onto the calculation sheet using the MS Excel program. A statistical analysis was performed to outline the structure of the group of patients analyzed. Frequency tables were used to analyze qualitative data. The quantitative data obtained were evaluated with the use of distribution parameters. In addition, the ANOVA one-criterion analysis was used. Values of $p \leq 0.05$ were considered statistically significant.

RESULTS

In a group of 70 patients, obesity was diagnosed (BMI >30 kg/m^2) in 10 patients (14.29%), 31 patients (44.29%) were overweight (BMI 25–30 kg/m^2) and 29 patients (41.43%), had normal weight (Tab. 1). One patient was reported to be underweight (BMI 18.18 kg/m^2), and was included into the normal weight group. In 5 patients, in the final months of observation, a less than 10% decrease in body mass was reported. In the majority of patients (n = 50, 71.43%) normal blood serum glucose levels (3.61–5.83 mmol/l) were noted. Incorrect fasting glucose (5.83–6.9 mmol/l) was observed in 16 patients (22.85%). The average BMI value for the whole group was 25.98 ±5.38 kg/m^2. The mean glucose serum level was 5.49 ±1.0 mmol/l and the average insulin level was within the normal range (626 μlM/ml), at 18.93 ±14.67 μlM/ml. The following phase of analysis was to search for differences in the obtained quantitative data, depending on the clinical grade (Tab. 2). No statistically significant differences between groups were reported with regard to the clinical grade. Higher insulin level (25.65 ±21.14 μlM/ml) was reported only in the group of patients in the 3rd clinical grade. In patients in the 1st clinical grade, insulin levels were 13.96 ±3.25 μlM/ml, in the 2nd grade 15.90 ±9.72 μlM/ml, and in the 4th grade 17.89 ±12.37 μlM/ml.

In terms of weight categories, no significant statistical differences in the analysis of average glucose and insulin levels were reported according to BMI values (Fig. 1). There were no significant differences between the average BMI, glucose and insulin serum levels in relation to tumor localization (Fig. 2–4).

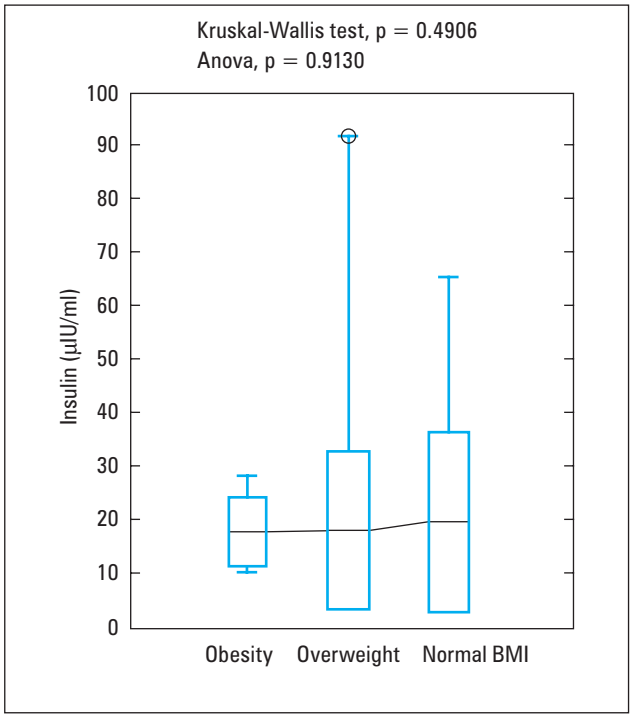

Fig. 1. Average insulin level in relation body mass index (BMI) in group of 70 patients

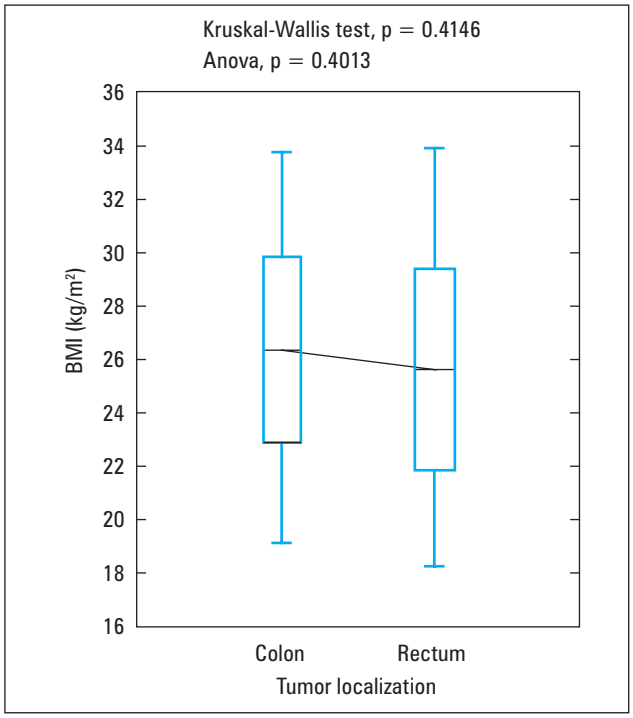

Fig. 2. Average value body mass index (BMI) in relation to tumor localization in group of 70 patients

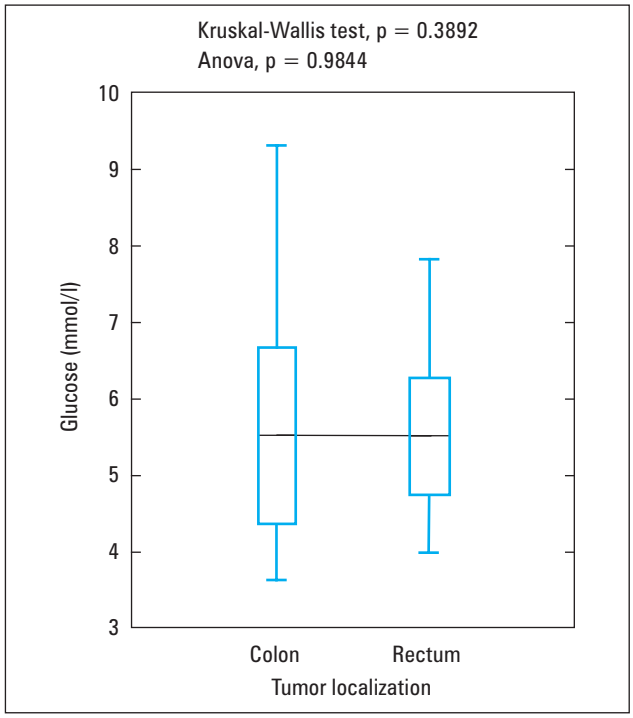

Fig. 3. Average glucose serum level in relation to tumor localization in group of 70 patients

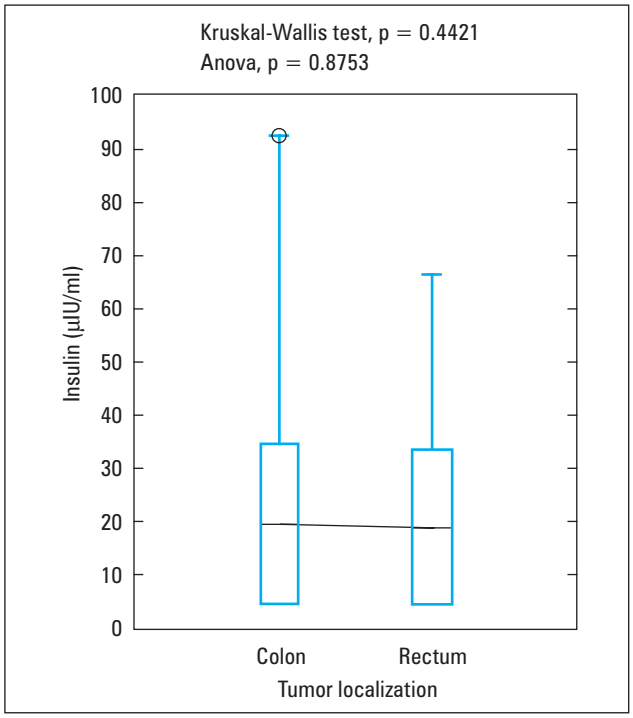

Fig. 4. Average insulin level in relation to tumor localization in group of 70 patients

Table 1. Clinical characteristics of patients (n = 70)

Characteristic	Analyzed group, n (%)	Men, n (%)	Women, n (%)
Number of patients	70 (100)	41 (58.57)	29 (41.43)
Average age (years)	65	65	66
BMI >30	10 (14.29)	4 (9.76)	6 (20.69)
25 ≤BMI ≤30	31 (44.29)	19 (46.34)	12 (41.38)
20 ≤BMI <25	29 (41.43)	18 (43.90)	11 (37.93)
Location of the cancer			
Colon	39 (55.71)	20 (48.78)	19 (65.52)
Rectum	31 (44.29)	21 (51.22)	10 (34.48)
Clinical stage according to TNM			
I T1N0M0 T2N0M0	14 (20.00)	11 (26.83)	3 (10.34)
II T3N0M0 T4N0M0	18 (25.71)	9 (21.95)	9 (31.03)
III T1N1M0 T2N1M0 T3N1M0 T4N1M0 T1N2M0 T2N2M0 T3N2M0 T4N2M0	22 (31.43)	10 (24.39)	12 (41.38)
IV TxNxM1	15 (21.43)	10 (24.39)	5 (17.24)
No data	1 (1.43)	1 (2.44)	0
Histopathological malignancy grading			
G1	11 (15.71)	5 (12.20)	6 (20.69)
G2	39 (55.71)	26 (63.41)	13 (44.83)
G3	2 (2.86)	1 (2.44)	1 (3.45)
Gx	14 (20)	6 (14.63)	8 (27.59)
No data	4 (5.71)	3 (7.32)	1 (3.45)
Histological type			
Adenocarcinoma	44 (62.86)	26 (63.41)	18 (62.07)
Adenocarcinoma mucinosum	6 (8.57)	3 (7.32)	3 (10.34)
Adenocarcinoma necroticans	3 (4.29)	2 (4.88)	1 (3.45)
Adenocarcinoma ex/muc	17 (24.29)	10 (24.39)	7 (24.14)
Coexistent diseases			
Cardiovascular diseases	31 (44.29)	16 (39.02)	15 (51.72)

BMI – body mass index

DISCUSSION

The results obtained in the current study should be interpreted with caution. The group of patients who took part in the study was too small and clinically heterogeneous. However, it should be noted that in the majority of analyzed patients too high body mass index was reported, which additionally determines the presence of impaired fasting glucose, insulin resistance, or undiagnosed type 2 diabetes.

On the basis of the current study it can be confirmed that body weight beyond the reference values is reported in several patients with colorectal cancer. Over half the patients were overweight or obese (BMI >25 kg/m^2). However, there were no reports of statistically significant differences involving average insulin levels depending on BMI. Higher average fasting insulin levels were reported in patients in the 3rd clinical grade of cancer, but with no significant statistical differences. The study was not performed among healthy subjects; thus

Table 2. Average and standard deviation for body mass index (BMI), glucose and insulin level in relation to clinical stages in the group of colorectal cancer patients (n = 70)

Clinical stage	I	II	III	IV
BMI (kg/m²) (mean ±SD)	25.19 ±2.37	26.39 ±4.51	26.21 ±3.43	25.56 ±3.57
Glucose (mmol/l) (mean ±SD)	5.64 ±0.51	5.49 ±1.04	5.77 ±0.99	5.34 ±1.27
Insulin (μlM/ml) (mean ±SD)	13.96 ±3.25	15.90 ±9.72	25.65 ±21.14	17.89 ±12.37

SD – standard deviation

variables can be compared only within the range of analyzed patients with colorectal cancer. Saydah et al. [18] evaluated the association of insulin serum level in the colorectal cancer patient group and the controls. The average insulin levels in both groups were not significantly different. The randomization of patients in terms of their clinical grade made the groups smaller, which also significantly limited the study. The clinical heterogeneity of the groups (coexistent diseases, age, sex, hormonal status) prevents the unequivocal summary and conclusions. However, the high insulin level reported in several patients may speak for its participation in proliferation processes through IGF1 secretion, as well as the activation of tyrosine kinase receptor by IGF1. Some researches indicate that obesity is associated with hyperinsulinemia and the development of type 2 diabetes, and stress the role of hyperinsulinemia in pathogenesis of colorectal cancer [19,20]. Insulin may initiate its metabolic action by its own receptor – IGF1R; however, by interaction with the receptor IGF1R insulin acts as a growth factor, leading to mitogen-activated protein kinase signaling cascade activation, the mitogenic effect, or phosphatidilinositol-3 kinase PI3K activation, which leads to the antyapoptical effect. Then the role of insulin activating the IGF1R receptor is similar to the role of IGF1, which is a recognized growth factor for many cancers. Multiple studies showed that patients with colorectal cancer are very often overweight or obese. Thus, it is necessary to consider adipose tissue-related growth factors in cancerogenesis and in the pathogenesis of this cancer. Adipose tissue, as the endocrine organ, produces many compounds of variable biologic activity, inter alia: tumor necrosing factor α, interleukin 6, transforming growth factor β, IGF1, adiponectin, leptin and others [21,22]. The reported increase of IGF1 is frequently connected with hyperinsulinemia, which is the additional unfavorable risk factor of colorectal cancer. The increase of IGF1 and present in colorectal cancer tissue receptors for IGF 1 favors carcinogenic proliferation. Furthermore, IGF1 stimulates the increase of vascular endothelial growth factor production, which is a crucial factor in angiogenesis and contributesto the development of the tumor.

The studies conducted so far unequivocally show an important role of metabolic disturbances prophylaxis. These disorders are not only risk factors of cardiovascular diseases, but also of cancers. The use of oral antidiabetic drugs in type 2 diabetes treatment is simultaneously important in cancer prevention [16,23]. Their activity consist in breaking insulin resistance and decreasing hyperinsulinemia, which inhibits the mitogenic action of insulin and insulin-like growth factors by minimizing the role of intracellular signal transduction activated by these factors.

We concluded that overweight and obesity were observed in most of the colorectal cancer patients, andno statistical differences were observed between insulin serum level and tumor localization.

ACKNOWLEDGEMENTS

This work was supported by grants of the Silesian Medical University.

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