Insulin-Like Growth Factor I (IGF-I) as a Sensitive Biomarker of Catabolism in Patients With Gastrointestinal Diseases

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Gastrointestinal ailments evoke changes in the hypothalamic-pituitary-adrenal (HPA) axis and modulation of hepatic protein synthesis. We examined the catabolic effect of certain primary gastrointestinal diseases and surgery on the concentration of insulin-like growth factor I (IGF-I). Blood samples from patients with gastric cancer (GC), cholecystitis (CC), or inguinal hernia (IH) were taken before and after surgery. The concentrations of IGF-I, IGF binding protein-1 (IGFBP-1), insulin, cortisol, and glucose were determined. In GC patients the concentration of IGF-I was reduced and the concentrations of IGFBP-1 and cortisol were elevated preoperatively; after surgery, IGFBP-1 normalized. In CC patients the

concentration of IGF-I was low and the concentration of IGFBP-1 was high before cholecystectomy; after surgery IGFBP-1 returned to normal and the concentration of cortisol increased. In IH patients the concentration of IGF-I was low and the concentrations of IGFBP-1 and cortisol were high before surgery; after laparotomy IGFBP-1 returned to normal. The metabolic changes were present in all analyzed patient groups, regardless of the severity of disease and nutrition. The concentration of IGF-I was reduced before surgery and remained reduced after, recommending IGF-I as a metabolic marker in both pre and postoperative examination of patients. *J. Clin. Lab. Anal.* 21:335–339, 2007. © 2007 Wiley-Liss, Inc.

Key words: IGF-I; metabolism; gastric cancer; cholecystitis; inguinal hernia

INTRODUCTION

Gastrointestinal ailments are associated with stress due to poor nutrition, tissue injury, trauma, and infection. The innate, nonspecific response known as the acute phase reaction is a prominent component and may develop from noninfectious causes. Released cytokines may contribute to the activation of the hypothalamic-pituitary-adrenal (HPA) axis and modulation of hepatic protein synthesis (1). The peripheral concentrations of some blood components significantly increase, while others decrease.

Insulin-like growth factor I (IGF-I), a potential biomarker of hepatic protein synthesis, is a peptide with a homologous structure to insulin. Insulin has predominantly metabolic actions, while IGF-I, as well as metabolic actions, is strongly mitogenic and regulates cellular proliferation and growth. Insulin and IGF-I signaling can induce very similar cascades of postreceptor signaling events (2). IGF-I in blood circulates mainly in complexes with IGF binding proteins (IGFBP), which

form a mobile reserve. Approximately 1% is free and potentially active, matching the concentration of insulin, whose reserve is stored in the pancreatic islets. Growth hormone (GH) is the principal regulator of hepatic IGF-I synthesis. The GH/IGF axis is sensitive to cytokine activity and nutritional variations (3). IGFBP-1 differs from the other IGFBPs in its rapid regulation according to the metabolic state of the organism. The blood level shows diurnal variation with increased release between meals and suppression following food intake (4). In healthy persons insulin potently suppresses IGFBP-1 synthesis. In response to hypoglycemia IGFBP-1 fulfils a

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counter-regulatory role by blocking the insulin-like activity of IGFs.

The purpose of this work was to examine the catabolic effect of certain primary diseases and surgery on the circulating concentration of IGF-I in comparison with other recognized markers in patients with gastrointestinal diseases.

MATERIALS AND METHODS

Blood samples from all persons were collected in the morning (8 AM), after overnight fasting (for at least 12 hr). Blood samples from patients with gastrointestinal diseases ($n = 63$, age 27–72 years, body mass index [BMI] 15–35 kg/m²) were taken in the morning prior to and in the morning after surgery. The patients were grouped according to their primary disease: 1) with gastric cancer (GC, $n = 17$, age 34–70 years, BMI 15–26 kg/m²; 13 patients had gastrectomia totalis and four had gastrectomia subtotalis); 2) with cholecystitis (CC, $n = 30$, age 27–70 years, BMI 24–35 kg/m²); and 3) with inguinal hernia (IH, $n = 16$, age 27–72 years, BMI 16–32 kg/m²). Patients in the first group were preoperatively graded as American Society of Anaesthesiologists (ASA) III (80%) and ASA IV (20%); most of them exhibited weight loss in the previous 3 months 2–10%, 70% underwent open surgery; and 30% had urgent surgical intervention. Patients in the second and third group were graded as ASA I (50%) and ASA II (50%); they had no hormonal, severe cardiovascular, respiratory, or metabolic dysfunctions and they were admitted to the hospital a day before laparoscopic surgery.

Biochemical analyses were performed in order to assess the general metabolic status of the patients (5). The concentrations of the following analytes were determined: IGF-I (RIA), insulin (RIA), cortisol (RIA), IGFBP-1 (immunoradiometric assay, IRMA), using INEP commercial kits (Belgrade, Serbia), and glucose (glucose oxidase-peroxidase aminoantipyrine method, GOD-PAP), using the Human reagent kit (Human, Wiesbaden, Germany).

The results obtained for the patients were compared to those obtained for healthy subjects ($n = 81$, age 20–75 years, BMI 16–32 kg/m²).

Data Analysis

The results of the measured parameters are expressed as the median and the reference interval (determined as the central 95% range between the 2.5th and 97.5th percentiles) as proposed by International Federation of Clinical Chemistry (IFCC) (6). To evaluate differences in the results between the groups, the Mann-Whitney test was performed. A Z-value greater than 1.96 ($P = 0.05$) was considered to be statistically significant. Data were analyzed by the statistical package Primer of Biostatistics (version 5, McGraw-Hill Companies, Dubuque, IA).

RESULTS

To assess the intensity of IGF-I and IGFBP-1 change in relation to insulin in healthy persons, a standardized oral glucose tolerance test (OGTT, 75 g glucose/0.2 L water) was performed in 22 volunteers included in our control group (7). The results are shown in Table 1. IGF-I concentration did not change significantly during OGTT. The concentration of insulin was the greatest 60 min after glucose intake and then decreased, approaching fasting level after 180 min. IGFBP-1 concentration was significantly reduced 120 min after OGTT started and continued further to drop at 180 min. Besides changing in opposite directions, the alterations in insulin and IGFBP-1 concentrations were phase-shifted.

In GC patients the concentration of IGF-I was significantly reduced and the concentrations of IGFBP-1 and cortisol were elevated preoperatively (Table 2). After surgery, the concentration of IGFBP-1 did not vary from the value obtained for the healthy group. The concentrations of glucose and insulin were not significantly different compared to the referent group.

TABLE 1. The concentrations of IGF-I, IGFBP-1, and insulin in healthy subjects during OGTT*

Time interval (min)	IGF-I (nmol/L)	IGFBP-1 (nmol/L)	Insulin (mU/L)
	Median (2.5th–97.5th percentile)	Median (2.5th–97.5th percentile)	Median (2.5th–97.5th percentile)
0	19.8 (13.1–22.6)	0.70 (0.09–1.52)	16.2 (7.7–24.4)
60	18.4 (10.9–22.0)	0.76 (0.10–1.38)	114.8 (19.5–252.4) ^b
120	17.5 (10.6–21.4)	0.34 (0.04–0.89) ^a	39.2 (13.1–127.0) ^b
180	17.1 (11.8–20.4)	0.17 (0.05–0.49) ^a	16.2 (13.7–49.6) ^a

*Results are presented as medians and the central 95% range between 2.5th and 97.5th percentiles.

^aStatistically significant difference between time intervals at $P < 0.05$.

^bStatistically significant difference between time intervals at $P < 0.0005$.

TABLE 2. Concentrations of IGF-I, IGFBP-1, insulin, cortisol, and glucose in healthy subjects and patients with gastrointestinal diseases prior to and after surgery*

	Healthy subjects		GC patients		CC patients		IH patients	
	Median (2.5th–97.5th percentile)		Median (2.5th–97.5th percentile)		Median (2.5th–97.5th percentile)		Median (2.5th–97.5th percentile)	
	Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery
IGF-I (nmol/L)	21.6 (10.8–41.2)	10.8 (4.0–19.3) ^c	11.2 (4.1–21.6) ^c	12.8 (6.0–22.1) ^b	15.2 (10.8–19.2) ^a	12.5 (9.3–20.0) ^b		
IGFBP-1 (nmol/L)	0.56 (0.04–1.61)	0.85 (0.60–2.07) ^a	0.56 (0.46–5.50)	0.89 (0.51–2.27) ^a	1.09 (0.56–2.20) ^a	0.85 (0.34–1.96)		
Insulin (mU/L)	14.0 (6.4–24.8)	10.5 (4.7–26.3)	12.8 (5.1–17.6)	12.1 (7.1–23.2)	9.5 (6.8–21.6)	10.5 (8.9–17.2)		
Cortisol (nmol/L)	322 (108–614)	539 (310–792) ^c	633 (290–1048) ^c	367 (160–707)	486 (366–760) ^b	558 (283–793) ^c		
Glucose (mmol/L)	4.8 (3.9–5.9)	5.0 (3.7–11.8)	5.4 (3.9–15.1)	5.2 (3.6–8.2)	4.4 (3.9–7.6)	4.9 (4.1–14.7)		

*Results are presented as median and the central 95% range between the 2.5th and 97.5th percentiles.

^aStatistically significant difference between healthy subjects and patients at $P < 0.05$.

^bStatistically significant difference between healthy subjects and patients at $P < 0.005$.

^cStatistically significant difference between healthy subjects and patients at $P < 0.0005$.

In CC patients, before laparoscopic cholecystectomy, the concentration of IGF-I was lower and the concentration of IGFBP-1 higher than in healthy persons (Table 2). After surgery the level of IGFBP-1 returned to normal, but the concentration of cortisol exhibited significant elevation. The concentrations of insulin and glucose were within the reference ranges.

In IH patients the concentration of IGF-I was significantly lower than in healthy group and the concentrations of IGFBP-1 and cortisol were higher before surgery. After laparotomy only IGFBP-1 concentration returned to normal (Table 2). The values of insulin and glucose did not vary from the referent.

DISCUSSION

Low serum IGF-I levels were found in patients during trauma, sepsis, burn injury (8), major abdominal surgery (9), and in critically ill patients on admission to an intensive care unit (10). According to Timmins et al. (11), increased proteolysis of the predominant IGFBP-3 appears to be the main mechanism causing low total circulating IGF-I levels. Recently, we have described reduced IGF-I and IGFBP-3 levels preoperatively in patients with acute CC and during gastrointestinal inflammation (12,13). Similar findings were reported by Eivindson et al. (14) in patients with active ulcerative colitis and Crohn's disease.

Both caloric and protein restriction can decrease IGF-I levels (15). Isley et al. (16) demonstrated a 36% reduction in IGF-I levels after a 5-day fast, while restriction of energy intake alone in healthy adults led to lower circulating IGF-I and IGFBP-3 and increased IGFBP-1 concentrations (17).

OGTT was performed in healthy people to evaluate the influence of overnight (12 hr) fasting and glucose intake on IGF-I, IGFBP-1, and insulin concentrations. As our CC and IH patients were not on a fasting diet more than a day before surgery, the nutrition restriction was expected to have similar effect as in healthy people. The measured concentrations of both IGF-I and IGFBP-1, however, differed significantly from the reference range before surgery and IGF-I remained low after surgery. According to the experimental data, high levels of IGFBP-1 in our patients were not a response to low levels of insulin or hypoglycemia. The concentration of cortisol was elevated in both groups of patients, suggesting low concentrations of IGF-I and high concentrations of IGFBP-1 to be a reflection of stress-related rise in cortisol (4). IGFBP-1 elevation may also be caused by the stimulatory action of cytokines, which are known to activate the HPA cascade, reduce GH secretion (1), and alter the pattern of protein synthesis by the liver (18). GC patients were found to

Fig. 1. Frequency distribution of the IGF-I values in healthy subjects and patients with gastrointestinal diseases prior to surgery.

have the lowest IGF-I levels and the highest cortisol levels. The analysis of the laboratory data together with preoperative clinical data, such as ASA score and weight loss, confirmed the severity of catabolism in studied subjects (Fig. 1) (19).

Among the parameters that were determined in this study, only the circulating concentration of IGF-I changed in all our patient groups before surgery and remained changed after. The baseline levels of IGF-I for each patient, in advance of the onset of a disease, were not available, since the concentration of the circulating IGF-I is not routinely measured in regular physical exams. As diet and age influence individual IGF-I concentration to certain extent, the baseline IGF-I level, obtained as an average of serial measurements within specific time interval, in advance of illness, would be more reliable initial information. Even without these specific data, the differences between patients and the control group were statistically highly significant and may be easier to see when the results are presented as a frequency distribution, as in Fig. 1 (the preoperative data for patients are shown). In the group of healthy persons, there was not a single IGF-I value lower than 11 nmol/L and almost 25% of the values were above 30 nmol/L. In all three groups of patients there were a considerable number of IGF-I values below 11 nmol/L and there was only one value above 25 nmol/L (for a patient in the CC group). The decreased concentration of IGF-I can be attributed to primary disease in the case of patients with CC and IH and, probably, due to the combined effects of primary disease and nutrition in the case of patients with GC. The concentration of IGF-BP-1, in general, was above the upper referent limit before surgery and normalized

after intervention, while the concentration of cortisol increased due to surgery.

IGF-I is, therefore, a sensitive indicator of catabolism whose concentration in blood diminishes even when some other nutritional and hormonal response markers do not change (glucose and insulin) or alter to a minor degree. IGF-I determination may be useful in assessing a general metabolism of a patient having gastrointestinal disease. As our results have documented, the metabolic changes were present in all analyzed patient groups, regardless of the severity of disease and normal nutrition. Thus, the level of IGF-I may be considered as a metabolic marker in both pre and postoperative examination of patients. The knowledge on the personal baseline level of IGF-I can certainly aid in precision when evaluating the degree of metabolic change.

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