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ARTICLESerum Insulin-Like Growth Factor-I and Tumor Size in  
Patients with Metastatic Liver Cancer

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**Background and Aims:** Insulin-like growth factor-I (IGF-1) is a liver-derived humoral factor, which has important anabolic and metabolic actions. Low serum concentrations of IGF-1 have been reported in patients with chronic liver disease, especially cirrhosis and hepatocellular carcinoma and metastatic liver cancer. The aim of our study was to evaluate any possible relationship between intensity of liver metastases on serum IGF-1 concentrations.

**Methods:** Serum IGF-1 were measured by ELIZA (III) in 10 patients with uninodular or multinodular liver metastases and extension  $\leq 50\%$  (group A) and 10 patients with multinodular or massive liver metastases and extension  $> 50\%$  (group B) of liver size without liver failure.

**Results:** Serum IGF-1 concentration was significantly lower in the more sever metastatic group (group B) than the less sever metastatic group (group A) ( $121.40 \pm 52.08$  vs.  $210.30 \pm 42.59$  ng/ml, respectively;  $P < 0.001$ ).

**Conclusions:** Our findings suggest that the states of serum IGF-1 levels in patients with metastatic liver cancer may be a helpful finding for determining the severity of metastasis to the liver.

**Keywords:** IGF-1, Metastatic Liver Cancer, Computed Tomography

## Introduction

Hepatic tumors may either originate in the liver or spread to the liver from primary lesions in remote or adjacent organs. In adults, hepatic metastases are more common than primary malignant tumors of the liver in most parts of the world <sup>(1)</sup>. The insulin-like growth factor (IGF) axis has important autocrine, paracrine, and endocrine roles in the promotion of growth and cell biology <sup>(2)</sup>. IGF-I and IGF-II are peptides that presumably are required for normal fetal and postpubertal growth and synthesized primarily by the liver <sup>(3, 4)</sup>.

Alterations of the IGF system have been implicated in the pathogenesis of several malignancies <sup>(5-9)</sup>. Although experimental studies have demonstrated an important role for IGF-1 in hepatocarcinogenesis, the clinical data regarding

IGF-1 in patients with liver malignancy are controversial, and correlation between IGF-1 and hepatocellular carcinoma or metastatic liver cancer has only been investigated in a few studies <sup>(3, 10-12)</sup>. These clinical studies have shown that IGF-1 is reduced in both primary and metastatic liver cancer

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(3, 11-13). This reduction has been attributed to the effect of damage to the liver parenchyma (3, 14, 15), but this reduction maybe not exclusively due to functional liver damage in hepatocellular carcinoma (13). The aim of our study was to evaluate the effect of size of liver metastases on serum concentrations of IGF-I independent of significant liver damage function.

### Patients and Methods

Between January 2004 and January 2005, adult cases of liver mass who were admitted to Taleghani Hospital in Tehran and registered in RCGLD were included in the study. The diagnosis of metastatic adenocarcinoma of liver was established on the basis of abdominal CT scan and biopsy under the guide of sonography. Patients with metastatic liver cancer were interviewed during their hospital stay by confidential questionnaires to obtain information relevant to their liver disease which included age, gender, clinical manifestations; and for ethical considerations, informed consent for blood sampling and usage of tissues was obtained from all patients.

Patients with liver tumor who had cirrhosis, low serum albumin levels, prolonged prothrombin time, a bilirubin level higher than 2 mg/dL, positive HBsAg or anti-HCV antibody (third-generation tests), signs of pituitary insufficiency or hypophyseal tumor, sepsis, renal insufficiency with serum creatinine higher than 1.5 mg/dl, hypothyroidism, prolong fasting, inflammatory bowel disease, and renal failure that change plasma IGF-I values or are believed to reflect functional liver damage were excluded from study groups through history, physical examination and standard laboratory tests.

From 52 cases of liver mass, a total of 27 patients with metastatic liver cancer in whom data were complete were identified. CT scan of these patients was re-evaluated by a radiologist chosen randomly, for determining tumor morphology and the largest cross-sectional area of tumor to the largest cross-sectional area of the liver ratio. The proportion of sum of low density areas (or tumor areas) in their largest section relative to largest cut section of the entire liver was taken as the size of tumor based on Okuda classification (16). Using tumor morphology index, our patients were divided into two groups. Group A with uninodular or multinodular metastases and extension  $\leq 50\%$  and group B with multinodular or massive metastases and extension  $> 50\%$  of liver size. Due to the effect of age on serum IGF-1 level, 10 age-matched patients were

randomly selected in each group.

Blood samples were taken from cubital veins before 8:00 a.m. after an overnight fasting and before any treatment was given, then blood was separated from serum within 3 hours. One ml coded samples were frozen and stored at  $-80^{\circ}\text{C}$  in the laboratory of the research centre of endocrinology in Taleghani Hospital. IGF-1 was measured in a random subset of the subject in ng/ml by ELIZA method (DRG, USA). The sensitivity was 0.15 ng/ml and IGF-1 level in a healthy adult was 150-350 ng/ml. IGF-1 as a continuous variable was compared between two groups, 10 cases with uninodular or multinodular liver metastases and extension  $\leq 50\%$  and 10 cases with multinodular or massive liver metastases and extension  $> 50\%$ . Statistical analysis was performed using the Mann-Whitney test for normality and Student's *t*-test was used to denote statistical significance.

### Results

From 52 cases of liver mass, a total 20 age-matched patients with MLC in whom complete data were compatible with our study identified in group A (10 patients) and group B (10 patients) were selected and included in the comparison between the IGF-1 level. Age, site of primary tumor and lab data of the two groups are described in Table 1. The Mann-Whitney test reported that the data was normally distributed with a mean of  $165.85 \pm 64.99$  ng/ml and by using student's *t*-test, there were striking differences among the two groups in the

**Table 1.** Clinical features of the studied patients.

	Group A	Group B
M:F ratio	6:4	7:3
Age (range) (yr)	51.9 $\pm$ 27 (24-79)	53.3 $\pm$ 26 (27-89)
IGF-1 (range) (ng/ml)	210.30 $\pm$ 42.59 (135-266)	121.40 $\pm$ 52.08 (46-230)
Albumin (g/l)	3.5 $\pm$ 0.2	3.4 $\pm$ 0.2
Prothrombin time (seconds over control)	1 $\pm$ 1	1 $\pm$ 1
Site of primary tumor		
• Colon	2	2
• Prostate	0	1
• Pancreas	2	1
• Stomach	4	4
• Unknown	2	2

Note. By using tumor morphology index our patients divided into two groups. Group A with uninodular or multinodular metastases and extension  $\leq 50\%$  and group B with multinodular or massive metastases and extension  $> 50\%$ . Values are expressed as mean  $\pm$  SD (P < 0.001).

serum level of IGF-1. The mean value among group A patients with MLC was approximately 43 percent higher than group B:  $210.30 \pm 42.59$  vs.  $121.40 \pm 52.08$  ng/ml. Statistically, there was also a significant difference ( $P < 0.001$ ) between two groups. It implies that in MLC patients, IGF-1 is reduced in more severe liver metastases based on size of metastases in CT scan independent of functional liver damage such as level of albumin and prothrombin time which were excluded from study. Individual IGF-1 levels of our group B patients decreased below normal range in adult (150-350 ng/ml) in all of them but two. It is necessary to notify that analysis of 27 patients without age- matching was also statistically significant.

## Discussion

The IGF is an important growth factor system involved in both the development of the organism and the maintenance of normal function of many cells (15, 17). IGF-I is synthesized by multiple mesenchymal cell types, and the liver is the source of most (75 percent) of plasma IGF-I (3, 4). The system also has powerful anti-apoptotic effects and evidence has accrued to demonstrate that the IGFs play an important role in cancer (17). Individuals with high serum IGF-I levels have a relative risk for developing or progression of hepatocellular carcinoma, breast, prostate, bladder, and colon cancer (10, 15, 17-22).

Other studies have shown that level of IGF-I mRNA in hepatoma is lower than that in the non tumorous liver control. This phenomenon is probably caused by the low expression of human growth hormone receptor in hepatoma tissues (4, 23), and deregulation of the IGF axis, including the autocrine production of IGFs, IGF binding proteins (IGFBPs), IGFBP proteases, and the expression of the IGF receptors, has been identified in the development of hepatocellular carcinoma (10). The presence of a metastatic disease to the liver is an important determinate of survival, and prognosis is inversely proportional to not only the presence of metastases but also the number and volume of metastases (24, 25). The IGF-I receptor is commonly (though not always) overexpressed in many cancers, and many recent studies have identified new signaling pathways emanating from the IGF-I receptor that affect cancer cell proliferation, adhesion, migration and cell death; functions that are critical for cancer cell survival and metastases (17) and also receptor for the IGF-1R and its ligands IGF-1 and IGF-2 play important roles in the maintenance of the malignant phenotype and

receptor levels in tumor cells correlated with metastasis to the liver and data suggest that IGF-1R can modulate several cellular functions which impact on the metastatic phenotype including invasion and liver colonization (26). This study supports the hypothesis that circulating IGF-I levels play an important role in tumor development and metastasis (26).

However, to our knowledge, no study has been undertaken to examine the relation of IGF-1 with size or extension of MLC regardless of liver function or extent of liver damage. The present study is relatively large for MLC with normal functional liver tests. The results of our analysis indicate that serum IGF-1 decreases in patients with more severe MLC. This finding was not unexpected because most IGF-1 is produced in the liver and both liver cancer and cirrhosis contribute to the destruction of liver parenchyma and IGF-1 serum levels inversely correlated with Child's classification (12, 27, 28). However, our results may be of importance in two areas. Firstly, because we excluded accepted causes or serologic markers of liver damage, such as cirrhosis, low serum albumin levels, prolong prothrombin time, and high bilirubin. The reduction of IGF-1 in group B of MLC explained solely on the basis of tumor size and indicates that, even in the absence of overt evidence of functional liver damage, IGF-1 may be substantially reduced depending on the size of metastases. In another study, findings suggest that an IGF-1 feedback system activates in patients with HCC, but not in patients with MLC, and reduction of IGF-1 observed in the MLC group (25 virus-negative patients), can almost totally be explained by liver destruction, whereas most of the IGF-1 reduction among patients with HCC cannot, and the mean value of IGF-1 was 110.8 ng/ml among patients with MLC that is lower than the mean value in our patients (165.85 ng/ml) that is probably due to more functional liver damage (3). Secondly, these values may have diagnostic or prognostic implications under certain conditions. A highly significant positive correlation ( $P < 0.001$ ) was evidenced between IGF-I levels and size of liver metastases in CT scan (which provide quantitative estimates of the hepatic functional capacity) independent of functional liver parameters.

In a study by Mazziotti *et al.* reductions in serum levels of IGF-1 correlate with the development of hepatocellular carcinoma in patients with hepatitis C related cirrhosis and this prospective study demonstrates 1) the development of HCC is accompanied by a significant reduction of serum IGF-I levels independent of the grade of impairment of liver function; and 2) modification of

the IGF-I level precedes the morphologic appearance of HCC, permitting a precocious diagnosis of the tumor<sup>(13)</sup>. Our data also suggest that, in MLC, the decrease of circulating IGF-I values is related to alterations of size of liver metastases, and that IGF-I can be used as a good indicator of severity of liver metastases. This finding is consistent with other studies which indicate that serum IGF-1 is decreased in HCC and MLC<sup>(3, 11-13)</sup> and with our results which suggest that this decrease in MLC is to a large extent independent of functional liver damage and dependent upon the size of metastases. These observations may indicate the existence of a feedback loop regulating serum IGF-1 levels either at the endocrine or paracrine level<sup>(29, 30)</sup>. The nature of this feedback system, however, is not fully understood and our findings suggest that the replacement of liver tissue by tumors may depress IGF-1 production.

In conclusion, we suggest that serum IGF-1 levels correlate with size of liver metastases. These results suggest that serum IGF-1 levels in patients with metastatic liver cancer may be a helpful finding of the severity of liver metastasis to the liver with diagnostic and prognostic implications but future prospective studies are needed with greater sample sizes.

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