Original Article

IGF-I concentration and changes in critically ill patients

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Abstract

BACKGROUND: Insulin-like growth factor 1 (IGF-I) is an anabolic growth factor that affects nitrogen balance and its changing trend is not clearly understood in critically ill patients. This study was carried out to evaluate the association between serum IGF-I levels and its changing trend in critically ill patients.

METHODS: In this nested case-control study, all consecutive patients admitted to the medical ICU of Rasoul-e-Akram and Firuzgar hospital (Tehran, Iran) from January through October 2008 were included. IGF1 concentration was measured within the first 24h of ICU admission and the fourth, seventh and tenth day since admission. Patients were followed until discharge from ICU or expiration.

RESULTS: The study population consisted of 90 patients (mean age: 58.01 ± 22.56), 31 (34.4%) of who died and 59 (65.6%) were discharged. On admission, 43 patients (47.7%) had low IGF-I levels, whereas 47 (52.3%) had normal or high levels. The concentration of IGF-I was not significantly different in every 4 measurements between expired and discharged patients. Significant decrease was seen between first to fourth day IGF-I concentration (p = 0.005). Changing trend was not statistically different in two groups of patients.

CONCLUSIONS: There was no relation between low IGF-I concentration on admission day and increased adverse outcome, but overall these patients had lower IGF1. No clear association was found between changing trend of IGF1 and mortality. Stress on admission time may cause decreasing pattern of IGF-I in the first 4 days of admission.

KEYWORDS: Intensive Care Units, Critical Illness, Insulin-Like Growth Factor I, Mortality.

Almost all patients admitted to intensive care unit (ICU) represent metabolic states such as hyper-metabolism, substrate use alternations and negative nitrogen balance.[1] If the stress level remains higher than the system capacity, pathological procedures like protein catabolism occur.[2] Although liver protein synthesis increases, metabolic changes can lead to major endogenous protein breakdown, associated with muscle wasting and shortness of immune system that may cause higher risk of nosocomial infection and reduced potential to repeal with additional stress.[3,4] The highest rate of this situation is during the first 10 days of critical illness,[5] while it is combined with malnutrition.[6] This condition may lead to mortality and may be one of the most prevalent causes of death in ICU.[7] This finding contributes that early detection of stress level and metabolic state allows

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in-time intervention to promote anabolism and reducing catabolism.[8]

Hormonal stress is one of the most influencing conditions that can also be easily evaluated. But there is no sign of considering this issue in most usable prognosis evaluation scoring like acute physiology and chronic health evaluation (APACHE).[9] A vast number of hormones have been suggested for this matter, e.g. cortisol, glucagon, insulin, growth hormone (GH), etc. However, these assays are complex, expensive and may not be available or within reach.[3] Furthermore, most of these hormones have pulsatile secretion and a single measurement is not reliable.

Insulin-like growth factor 1 (IGF-I) is an anabolic growth factor,[10] primarily synthesized in liver and mainly stimulated by GH,[11] but can be regulated by many factors such as glucose concentration and nutrition.[12] IGF-I has an important role in cell proliferation, apoptosis and of course metabolism of protein, glucose, GH and insulin.[11-13] On the other hand, protein catabolism in critically ill patients such as traumatic and septic patients is associated with complex alternation in GH/IGF-I axis.[14,15] Unlike other hormones, IGF-I assays are less expensive and easier to do.[16] Thus, IGF-I measurements can be a better way to evaluate nitrogen balance of patients admitted to ICU.

Studies carried out to find association between IGF-I and patients prognosis have had controversial results. Kyle et al showed that IGF-I levels were lower in moderate and high stressed patients,[17] while Hu et al demonstrated that plasma IGF-I levels had no association with all-cause mortality in ICU.[18] Recent studies also showed no association between plasma IGF-I levels and mortality in critically ill patients with congestive heart failure [19] and acute renal failure.[20] But Guimarães et al showed that decreased levels of IGF-I and cholesterol were clearly related to higher mortality.[21]

All previous studies have been done on small samples of patients. Furthermore, no study has investigated changes of IGF-I concentration during ICU admission with an appropriate sample size.

For further investigation, this study was carried out to evaluate the association between serum IGF-I levels and its changing trend in ICU. The aim was to demonstrate that serum IGF-I levels may be a suitable prognostic factor for critically ill patients who may need more evaluation and care.

Methods
Patients
In this nested case-control study, 90 consecutive patients admitted to the medical ICU of the university teaching hospitals from January through October 2008 were included. The patients mostly suffered from pulmonary diseases (pneumonia [n = 4, 4.4%], chronic pulmonary obstructive disease [n = 4, 4.4%]), infectious diseases (septic shock and sepsis [n = 13, 14.4%]), and cerebrovascular accidents (n = 9, 10%).

Verbal consent was obtained from all patients (or from their next of kin) after detailed explanations and a letter of information was also given. This investigation has been approved by ethical committee of the University.

Assessments
At admission time, baseline clinical variables including age, sex, APACHE II score, and disease diagnosis were recorded. The APACHE II score incorporates acute physiologic variables and chronic health evaluation into a measure of the risk of in-hospital mortality.[9] History of other diseases was considered. Length of stay in the ICU was also recorded. The clinical endpoint was death or discharge from the ICU at any time during hospitalization.

IGF-I concentration was measured within the first 24 hours of ICU admission and the fourth, seventh and tenth day since admission. This was suggested by the ICU team and was based on their clinical judgment. The IGF-I concentration was evaluated using radioimmunoassay. On the basis of the company instructions, the concentration less than 107 is considered low, and 107 to 310 ng/ml is normal range of this assay, but on the basis of research results, the normal values are 95 to 249

ng/ml.[22,23] For IGF-I concentration, about 2-3 cc blood were obtained and centrifuged; then the serum was separated and sent for measurement of IGF-I in a private laboratory with a kit, on the basis of double sandwich ELISA (AssayMax, Missouri, USA). Intra-assay and inter-assay coefficients of variation were 4.8% and 7.2%, respectively.

Because of a laboratory fault, 1 patient did not have IGF-I level measured at admission, but IGF-Is were measured on days 4, 7 and 10; these data were included in the analysis. Out of all patients, 44 had the first two, 28 had the first three, and 20 patients had all four serial measurements for IGF-I. Patients discharged from the ICU or patients who died were not measured for IGF-I.

Statistical Analysis

Baseline characteristics of the low and normal IGF-I groups were compared using the Pearson chi-square test. Continuous variables were compared using the Student's t-test for normally distributed variables and the Mann-Whitney U test when either of these conditions was not met. Serial measurements were compared using the paired t-test. For evaluation of trend of changes in IGF-I during ICU admission, multiple measurement ANOVA analysis was carried out. The Log-Rank method was done to compare patient survival in the Kaplan-Meier analysis. Summary data are presented as mean ± SD. P values less than 0.05 were considered significant.

Results

Baseline Characteristics

The study population consisted of 90 patients admitted to ICU over a period of 12 months. It consisted of 51 men and 39 women, with the age range of 15 to 100 years (mean ± SD = 58.01 ± 22.56). On admission, 43 patients (47.7%) had low IGF-I levels, whereas 47 (52.3%) had normal or high levels. Out of all patients, 31 (34.4%) expired and 59 (65.6%) were discharged.

There was no significant difference between the two groups with low and normal or high IGF-I in some baseline characteristics, including Glasgow Coma Scale (GCS), PaO2 and etc. on admission. However, significant differences were found between groups in age and serum potassium level (Table 1).

Table 1. Characteristics of 89 critically ill patients on admission in the first IGF-I measurement

	Low IGF-I n = 83	Normal or high IGF-I n = 35	P value
Age (years old)	65.95 ± 18.04	51.44 ± 24.27	0.003
APACHE II	22.56 ± 6.38	24.22 ± 7.94	0.377
Mean arterial pressure (mmHg)	94.21 ± 14.06	90.05 ± 9.86	0.124
Heart rate (beats/minute)	94.51 ± 19.25	91.20 ± 17.74	0.418
Respiratory rate (per minute)	22.23 ± 4.05	20.74 ± 4.79	0.139
PaO2 (mmHg)	80.74 ± 48.66	91.47 ± 42.74	0.343
FiO2 (%)	66 ± 25	69 ± 31	0.625
HCO3 (mmol/L)	23.38 ± 7.85	25.30 ± 9.62	0.383
Sodium (mmol/L)	141.51 ± 6.34	139.90 ± 5.14	0.221
Potassium (mmol/L)	4.07 ± 0.48	4.31 ± 0.52	0.043
Creatinin (mg/dL)	1.47 ± 1.32	1.51 ± 1.43	0.899
Hematocrit (%)	33.64 ± 8.15	37.18 ± 9.83	0.078
White blood cell count (per mililiter)	13.27 ± 5.62	12.99 ± 3.73	0.795
PH	7.37 ± 0.08	7.35 ± 0.09	0.386
Systolic blood pressure (mmHg)	127.66 ± 19.17	120.82 ± 15.69	0.079
Diastolic blood pressure (mmHg)	77.48 ± 12.27	74.66 ± 7.80	0.217
GCS	9.71 ± 4.31	9.60 ± 5.05	0.910
Blood sugar at day before admission (mg/dL)	117.92 ± 25.91	168.43 ± 62.63	0.080
Blood sugar on admission day (mg/dL)	134.38 ± 38.19	151.94 ± 84.39	0.437
Male/female (ratio)	22/21	29/16	0.207

PaO2: Arterial O2 Tension; FiO2: Fraction of Inspired Oxygen; HCO3-: Bicarbonate; GCS: Glasgow Coma Scale

The concentration of IGF-I was not significantly different in every 4 measurements between dead and discharged patients. (Table 2)

IGF-I levels did not differ significantly between different diseases. Also there was no significant difference between different patients' groups in IGF-I concentration.

No difference was seen between APACHE-II scores of patients with first day IGF-I concentration lower and higher than our cut-point. (22.56 ± 6.38 ng/ml vs. 24.22 ± 7.94 ng/ml, p = 0.377).

Also, correlation between IGF-I (in all four measurements) and APACHE II score was not significant (p > 0.05).

Serial Measurements of IGF-I and Mortality In The ICU

A significant correlation between measurements of IGF-I in the a significant difference was seen between first and fourth day IGF-I concentration (113.91 ± 92.96 ng/ml in the first day and 85.45 ± 88.78 ng/ml in the fourth day, p = 0.005). The changing trend could be seen in figure 1 in all patients (A) and two groups with different outcome (B). No useful fact about the changes in patients could be found, nor association of IGF-I concentration in 10 days with

mortality was significant (Table 3).

Survival Analysis

The Survival rate of patients with low IGF-I on the first, fourth and tenth day of admission were 95%, 85% and 70%, respectively and in patients with normal or high IGF-I levels were 93%, 81% and 70%, respectively. The estimated mean survival time of patients with low IGF-I concentration was 34.25 (SE = 11.4) days and it was higher than the other group with a mean survival time of 21 (SE = 3.28) days, but this difference was not significant (p = 0.677) (Figure 2).

Discussion

Based on the results, an ambiguous association was found between the IGF-I and outcome. Concentration of IGF-I was low in most of the patients on admission day and later in ICU. In our study, there was no relation between low IGF-I concentration on admission day and increased adverse outcome, even a higher survival (although not significant) was found in patients with low IGF-I. The association of IGF-I on admission day and patients' prognosis was unclear, though there are controversies in the literature.[17-21]

Table 2. Blood concentration of IGF-I in dead and discharged patients (mean ± SD) (ng/ml)

Diagnosis category	IGF-I in 1st day (ng/ml)		IGF-I in 4th day (ng/ml)		IGF-I in 7th day (ng/ml)		IGF-I in 10th day (ng/ml)	
	< 107	> 107	< 107	> 107	<107	> 107	<107	> 107
Cardiac	4	2	2	0	1	0	0	0
Pulmonary	5	8	3	0	3	0	2	1
Endocrinology	0	1	0	0	0	0	0	0
CNS	9	11	11	3	6	2	2	0
Nephrology	1	3	0	1	0	0	0	0
Trauma	4	8	3	4	2	2	2	2
Gastroenterology	1	0	0	0	1	0	0	0
Hematology	1	2	0	0	0	0	0	0
Infectious	10	6	13	2	9	4	8	2
PNS	0	2	1	1	0	2	0	1
Surgery	0	1	0	0	0	0	0	0
Malignancy	4	1	1	0	0	0	0	0
Arrest	0	1	0	1	0	0	0	0
No diagnosis	5	3	4	0	1	0	1	0
Total	43	46	38	12	23	10	15	6

Table 3. Mortality rate based on IGF-I concentration in different measurements

IGF-I	Dead	Discharged	P value
1ˢᵗ day IGF-I	135.91 ± 118.50	124.99 ± 96.23	0.657
4ᵗʰ day IGF1	79.84 ± 59.34	87.67 ± 101.62	0.779
7ᵗʰ day IGF-I	89 ± 65.89	96.56 ± 66.39	0.763
10ᵗʰ day IGF-I	76.66 ± 73.03	86.06 ± 59.39	0.769
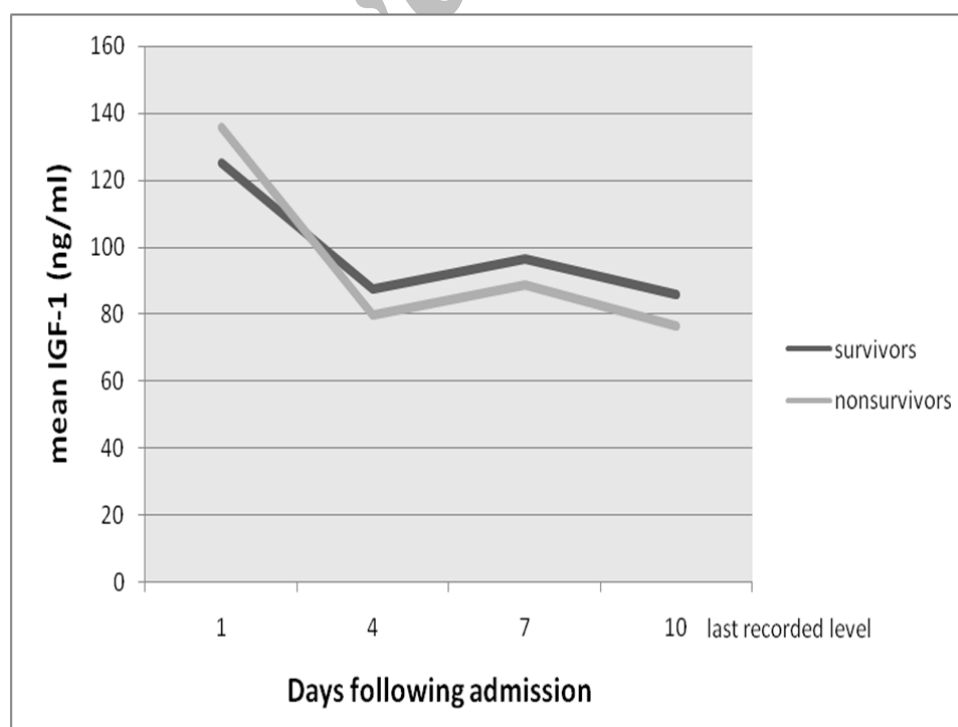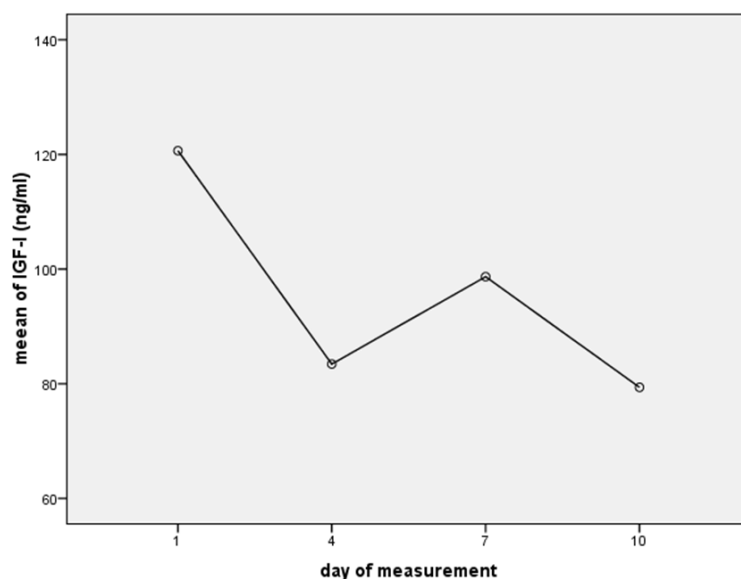
Figure 1. (A) Serial measurements of IGF-I for 20 patients and (B) trend in IGF-I levels over four times in two groups of patients that died or were discharged (20 patients)

Survival Functions
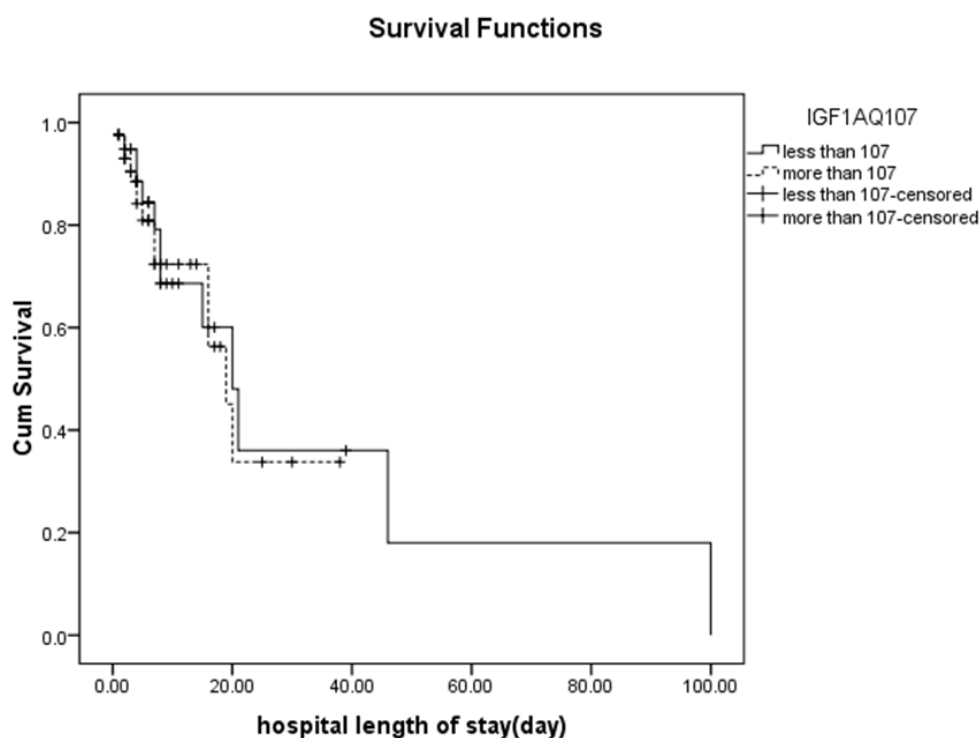
Figure 2. Patients' survival (p = 0.677)

The decreasing pattern of IGF-I in the first 4 days of admission (the second measurement in comparison with the first one) could suggest effect of stress on IGF-I in the first days, when the patient may not be prepared to confront stress. Stress conditions are known to disturb the GH- IGF-I axis.

This consist a biphasic pattern. The initial stress response consists of activated GH release whereas circulating level of GH-dependent IGF-I fall. 'In contrast, in the chronic intensive care-dependent phase of severe illness, pulsatile GH secretion substantially decreases whereas the non-pulsatile fraction remains relatively elevated, resulting in an abnormal flat GH secreting pattern and low-normal mean nocturnal GH serum concentrations. Specifically the reduced amount of GH released in pulses is found to be related to low circulating levels of IGF-I, IGF Bonding Protein-3 and acid-labile subunit, which suggests that a relative hyposomatotropism may participate in the pathogenesis of the wasting syndrome distinctively in the chronic phase of critical illness.'[24]

Wasting syndrome "results from both an increase in muscle protein degradation as well as a decreased rate of both myofibrillar and sacroplasmic protein synthesis. This protein imbalance may be caused by an increased presence or activity of various catabolic agents, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), or glucocorticoids" other than mentioned low concentration and enhanced resistance of GH, IGF1 and other anabolic factors.[7,25,26] These results in "increased protein turnover and negative nitrogen balance. Severe catabolism leads to end-organ dysfunction and muscular weakness and make the need for mechanical ventilation" longer than usual.[27]

Protein loss in wasting process "leading to reduced lean body mass is recognized to contribute to the high levels of morbidity and mortality, seen in critical illness."[7]

This study was designed to evaluate the IGF-I changes during ICU admission in addition to baseline concentration of IGF-I.

The changing trend of IGF-I levels in this study was not significant in patients admitted to ICU. Furthermore, difference in the IGF-I changing trend was not significant between the two groups with different outcome. In previous

studies, recovery in survived patients has been associated with increasing IGF-I and IGF binding protein 3 concentrations and cessation of protease activity and increased levels of anabolic hormones,[25,28] but a recent study indicated that the patient with the best anabolic parameters may not necessarily be the most favored to survive in ICU.[29] Association of IGF-I changes in critically ill patients is not well known.

Catabolism cannot be prevented with standard parenteral or enteral nutrition formulas. In some studies, prescription of GH is suggested for critically ill patients to prevent catabolism. A recent multinational randomized controlled trial revealed that increased mortality of critically ill patients following administration of recombinant growth hormone could be caused by the negative effect of GH on IGF-I secretion.[27]

The primary disease on admission did not have significant association with the concentration of IGF-I, or the everyday blood sugar in this investigation. There are a few studies on catabolic response and pituitary axis dysfunction and low concentration of IGF-I in different patients admitted to ICU. Low IGF-I concentration has been reported in the patients with severe trauma, infection, severe brain trauma, heart surgery and abdominal surgery but the real significance of these findings still needs to be elucidated.[27,30,31]

Based on our findings, no difference was seen in the concentration of IGF-I between the two groups of patients with different outcome. Moreover, no association was seen between IGF-I and predictors of outcome like APACHE. Based on the calculated power, these could be due to small sample size (power = 0.5).

There is some evidence about better outcome in females that is associated with higher anabolic hormones and more stable pulsatility and regularity pattern of GH and concomitantly IGF-I levels.[25,32]

There are some limitations in the present study and the most important one is the high number of lost patients. The other limitation is that other hormones like insulin and GH and the drugs that affect their levels has not been evaluated to find the relation between these hormones in this situation. Further practical and detailed studies are recommended to clarify these issues. It is also recommended to perform other studies with a higher sample size of ICU-patients focusing on a subgroup of baseline disease and checking for other hormonal biomarkers.

Conclusions

Despite the low concentration of IGF-I in most patients admitted to ICU, no clear association was seen between IGF-I levels with outcome and other associated factors of outcome. Several reviewed studies have shown controversy in the relation of IGF-I with adverse outcome and diseases. Designing a multi-center investigation to evaluate the association of these variables is suggested.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

SH was the chief supervisor, idea creator and wrote the primary protocol. MEK was the second supervisor and helped improving the data and the protocol. SG and SRJK were responsible for writing the protocol, data collection, data analysis, writing the manuscript and submission follow-up. NSM and ASS were responsible for writing the protocol, data collection and writing the manu-

script. GG, MM, RM, MN and MRK helped in developing the protocol, data collection, writing, and revising the manuscript. All authors have read and approved the content of the manuscript.

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