Insulin-like growth factor-1 positively associated with bone formation markers and creatine kinase in adults with general physical activity

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Abstract
Background: The Insulin-like growth factor-1 (IGF-1) is primarily synthesized by hepatocytes in a growth hormone (GH)-dependent manner, it is also produced by bone and muscle. The effects of exercise on the associations between IGF-1 levels and bone turnover markers (BTM) were found in the previous studies. However, the associations between the levels of IGF-1 and BTM, liver function tests, and skeletal muscle markers in adults with general physical activity were not clear.

Methods: Ninety-four participants were recruited from healthy survey. Blood samples were collected to analyze the levels of IGF-1, total protein (TP), albumin (Alb), total bilirubin (T-Bil), direct bilirubin (D-Bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bone alkaline phosphatase (BALP), lactate dehydrogenase (LDH), creatine kinase (CK), creatinine (CRTN), and glucose. Urine samples were collected to analyze the CRTN and deoxypyridinoline (Dpd) levels.

Results: The positively significant associations were found between the IGF-1 levels and the levels of ALP, BALP, and CK, respectively. No significant associations were found between the IGF-1 levels and the levels of TP, Alb, A/G, T-Bil, D-Bil, AST, ALT, LDH, glucose, urinary CRTN, urinary Dpd, and Dpd/CRTN ratios, respectively.

Conclusion: The serum IGF-1 levels associated with the levels of skeletal muscle and bone formation markers (BFM), not the bone resorption markers under general physical activity in the healthy adults. The physician needs to consider the effects of bone formation and skeletal muscle markers on the IGF-1 levels in the management of IGF-1-related disorders.

Keywords
alkaline phosphatase, bone alkaline phosphatase, bone turnover markers, creatine kinase and bone formation markers, insulin-like growth factor-1
1 INTRODUCTION

Insulin-like growth factor-I (IGF-1) performs its activity after birth when the liver becomes its main source and under the control of growth hormones (GH), which plays a critical role in all aspects of skeletal development and bone remodeling by promoting the proliferation, differentiation, and function of chondrocytes, osteoblasts, and osteoclasts. There was a strongly negative correlation between plasma IGF-1 levels and hepatic injury and the circulating IGF-1 levels may have predictive value for determining hepatic damage in diabetic rats. Moreover, it is being increasingly noticed that patients with liver disease develop bone loss that can result in fracture and affect the life quality. Langlois et al. showed that the correlation between circulating IGF-1 levels and bone mineral density (BMD) was relatively strong. Many bone turnover markers (BTM) including bone formation and bone resorption involved bone development. Serum bone-specific alkaline phosphatase (BAP), osteocalcin (OC) and C-terminal or N-terminal propeptides of type I procollagen (PICP; PINP) were bone formation markers, however, urinary deoxypyridinoline (Dpd), serum carboxy-and amino-terminally cross-linked telopeptides of type I collagen (CTX and NTX) and Tartrate-resistant acid phosphatase 5b (TRAP5b) were regarded as bone resorption markers in clinical performance. Recently, the interactions between bone and skeletal muscles via local and humoral signaling pathways in addition to their musculoskeletal function were found, even if the mechanisms related to the interactions between skeletal muscles and bones remain unclear.

Low-circulating IGF-1 levels were associated with hepatic steatosis, and the association in patients with increased alanine aminotransferase (ALT) levels was stronger than that in patients without increased ALT levels. After participating in an eight-week high-force eccentric-cycle ergometry program, the subjects had higher serum creatine kinase (CK) levels and muscle IGF-1Ea (a muscle-specific isoform of IGF-1) than those before. In recent study, the circulating IGF-1 levels were significantly higher in the obese patients than those in the controls, and the significant association of BAP levels with IGF-1 levels was found in the obese patients. The positive associations between the IGF-1 and the risks of breast cancer, papillary thyroid cancer, and prostate cancer were found in the previous studies, but the risk of gastric cancer decreased in the individuals with IGF-1 gene rs2195239 polymorphism. Nevertheless, no significant difference of IGF-1 levels between the breast cancer patients and the controls was found in our previous study and another studies. In addition to the influences of menopausal statuses, racial variations, gene polymorphism, and subtypes of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2), the associations between the IGF-1 levels and biomarkers of skeletal muscles, liver function and bone modulation were worthy to investigate. Above-mentioned studies, the associations between the IGF-1 levels and biomarkers of skeletal muscles, liver function and bone modulation were shown in the participants with exercise programs or the patients with hepatic and metabolic diseases. In this study, the associations among them were investigated in the healthy adults with general physical activity. The associations of the biomarkers of skeletal muscles, liver function, and bone modulation with the circulating IGF-1 levels in the management of IGF-1-related disorders need to be evaluated.

2 MATERIALS AND METHODS

2.1 Subjects

Ninety-four participants including 35 males and 59 females (ages: 21–73 years, mean: 44.6 years) were recruited from healthy survey of a Kaohsiung Medical University Hospital. Those with the cancer histories, diabetes mellitus, hypertension, immunodeficiency disease, or inflammatory signs were excluded from the present study. This study was approved by the Ethics Committee of the Kaohsiung Medical University Hospital (KMUH-IRB-940225), and the informed consent of the subjects was obtained.

2.2 Sample collections and analysis

Blood samples were collected from all participants after an 8-hour fasting period in plain tubes and centrifuged at 2500 rpm for 10 minutes as soon as they had been collected. Prolonged exposure of the samples to light, especially direct sunlight, was avoided. The serum was separated immediately and stored at -20°C until used for assay. Stored serum samples were assayed within one week after sampling. Urine samples were collected between 9 and 11 am. Borate (1 g/L) was added to urine samples to prevent bacterial growth. The urine samples were stored at -20°C until analyzed.

Urine creatinine (CRTN) levels and serum total protein (TP), albumin (Alb), total bilirubin (T-Bil), direct bilirubin (D-Bil), aspartate aminotransferase (AST), ALT, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), CK, CRTN, and glucose levels were measured by the Beckman Synchrone CX-7 analyzer (Beckman Coulter Inc., Fullerbon, CA, USA). The TP and Alb levels were analyzed by the Biebu and bromocresol green (BCG) methods, respectively. The T-Bil and D-Bil levels were analyzed by the Diazo method. The AST, ALT, ALP, CK, and LDH levels were analyzed by the UV-kinetic method. The urine and serum CRTN levels were analyzed by the Jaffe's reaction. The glucose levels were analyzed by the HK/G6PD method.

Serum BALP level was measured by the Access Ostase assay (immunoassay method) by the Access II analyzer (Beckman Coulter Inc., Fullerbon, CA, USA).

Serum IGF-1 level was determined by the solid-phase, enzyme-labeled chemiluminescent immunoassay by DPC's IMMULITE 2000 (Diagnostic Products Corporation, CA, USA).

Urinary Dpd levels were measured by enzyme immunoassay on microtiter plates using reagents (Pyrilin R5 TM-D) supplied by the manufacturer (Metra Biosystems, France).
2.3 | Statistical analysis

Data were expressed as mean ± standard deviation (SD). The associations between IGF-1 levels and the levels of TP, Alb, A/G, T-Bil, D-Bil, I-Bil, AST, ALT, ALP, BALP, LDH, CK, glucose, urinary CRTN, urinary Dpd, and Dpd/CRTN ratio were performed by using simple regression. The alpha-level 0.05 was used to distinguish the difference in statistical significance.

3 | RESULTS

The IGF-1 levels and the levels of TP, Alb, A/G, T-Bil, D-Bil, I-Bil, AST, ALT, ALP, BALP, LDH, CK, glucose, urinary CRTN, urinary Dpd, and Dpd/CRTN ratios were shown in the Table 1. As shown in the Table 1 and Figure 1, the positively significant associations were found between the IGF-1 levels and the levels of ALP, BALP and CK, respectively (r=0.0071, 0.00032 and 0.023, respectively). Moreover, the association between the levels of BALP and IGF-1 was stronger than that between the serum IGF-1 and ALP levels. The associations between the IGF-1 levels and the levels of TP, Alb, A/G, T-Bil, D-Bil, I-Bil, AST, ALT, LDH, glucose, urinary CRTN, urinary Dpd, and Dpd/CRTN ratio were not significant (p>0.05).

TABLE 1 Correlations between the IGF-1 levels and the levels of TP, Alb, A/G, T-Bil, D-Bil, I-Bil, AST, ALT, ALP, BALP, LDH, CK, Glucose, urinary CRTN and urinary Dpd and Dpd/CRTN ratios in the healthy subjects

| Parameters | subjects (N=94) | r | p-values* |
|------------|----------------|---|-----------|
| IGF-1 (ng/mL) | 256.2±142.7 |     |           |
| TP (gm/dL) | 7.17±0.4 | 0.127 | 0.224     |
| Alb(gm/dL) | 4.13±0.3 | 0.134 | 0.196     |
| A/G | 1.37±0.2 | 0.053 | 0.612     |
| T-Bil (mg/dL) | 0.89±0.33 | 0.058 | 0.580     |
| D-Bil (mg/dL) | 0.11±0.06 | -0.0005 | 0.996     |
| AST (IU/L) | 26.55±13.8 | -0.128 | 0.218     |
| ALT (IU/L) | 31.13±42.26 | -0.05 | 0.629     |
| ALP (IU/L) | 60.4±25.36 | 0.276 | 0.0071    |
| B-ALP (ug/L) | 12.59±8.95 | 0.363 | 0.00032   |
| LDH (IU/L) | 149.55±27.76 | 0.023 | 0.825     |
| CK (IU/L) | 132.86±102.37 | 0.235 | 0.023     |
| Glucose (mg/dL) | 93.29±12.96 | -0.034 | 0.745     |
| Urinary CRTN (mM) | 12.92±7.53 | 0.161 | 0.121     |
| Urinary Dpd (nM) | 6.52±2.1 | 0.190 | 0.067     |
| Dpd/CRTN (x10^-4) | 6.52±2.11 | 0.082 | 0.42958   |

Results were expressed as mean ±SD

*p-values represented the associations between the IGF-1 levels and the levels of TP, Alb, A/G, T-Bil, D-Bil, AST, ALT, ALP, BALP, LDH, CK, Glucose, urinary CRTN and urinary Dpd and Dpd/CRTN ratios, respectively.

4 | DISCUSSION

Several factors affect the interactions between skeletal muscle and bone, the factors include genetic factors, aging, circadian rhythm, nutrition, mechanical factors, and endocrine factors such as IGF-1. The IGF-1 is primarily produced by the liver in a GH-dependent manner, but many of the tissues such as bone and skeletal muscle make their own IGF-1 by autocrine and paracrine signaling. Exercise-induced mechanical loading may positively influence bone through the stimulation of IGF-1 secretion from skeletal muscle, in spite of the roles of GH/IGF-1 axis in the interactions between skeletal muscle and bone are not fully understood. A 3-year follow-up study demonstrated that IGF-1 levels significantly positively associated with the BMD at both baseline and follow-up. Recently, the review articles revealed that the BMD and bone elongation increased by the actions of IGF-1 on skeletal acquisition through stimulation of extracellular matrix production and growth plate through regulation of cell proliferation and differentiation. In this study, there was positively significant correlation between the serum IGF-1 and ALP levels in healthy population, but negative correlation was found between serum IGF-1 and AST levels even though the correlation was not statistical significance. It was consistent to the study of Su et al. that serum IGF-1 levels were positively correlated with serum ALP levels, but were inversely correlated with serum AST levels in the healthy subjects. In additional, the serum IGF-1 level was not significantly correlated with the serum levels of TP, Alb, T-Bil, D-Bil and ALT in the present study. We infer that the interactions between the serum levels of IGF-1 and liver function tests were not found in the healthy population.

The increased serum IGF-1 levels were observed in elite athletes immediately after a maximum exercise test. It may be due to the muscle damaging exercise result in local up-regulation of IGF-1. IGF-1 plays an important role in myoblast proliferation, differentiation, and fiber formation after skeletal muscle damage. Therefore, muscle CK efflux and serum CK levels significantly increased after exercise, but depended on the type of exercise. In this study, the positive and significant correlation between the IGF-1 and CK levels was also found in adults with general physical activity.

IGF-1 actions are regulated by IGF-binding proteins (IGFBPs), which are secreted from muscle and may act on bone. Moreover, Tsujiya et al. suggested that high-force eccentric exercise-induce IGF-1 may activate OC and NTX in acute response. Although the different types of exercise resulted in the various effects of exercise on the IGF-1 levels and bone markers, the effects of exercise on the associations between IGF-1 levels and BMD were found in the previous studies. However, most of the patients who received blood sampling for clinical diagnosis or monitor were under general physical activity. Therefore, the strong positive associations between the IGF-1 levels and the bone formation marker PINP or the bone resorption marker CTX in young men and women (<55 years old) were shown in the general adult population. However, the IGF-1 levels were positive and significant association with the serum levels of PINP and BALP, not...
with the serum CTX levels in premenopausal women were shown in the previous study. Likewise, circulating IGFR-1 was associated with bone formation markers in postmenopausal women, but not with CTX levels. IGFR-1 enhances bone collagen and matrix synthesis and stimulates the replication of cells from the osteoblast lineage. The results of the previous studies were consistent to our results, which the IGFR-1 levels were positive and significant correlations with ALP and BALP levels, however, the urinary Dpd levels and Dpd/CRTN ratios were not significantly correlated with serum IGFR-1 levels without restriction of ages. In the previous study demonstrated that the urinary Dpd/CRTN ratio was found as a useful marker for bone metastasis caused by breast cancer and Dpd can be useful in evaluating therapeutic response. However, the serum IGFR-1 levels associated with bone formation markers, not bone resorption marker under general physical activity in the healthy adults in this study. In our knowledge, the associations between the serum IGFR-1 levels and urinary Dpd levels or Dpd/CRTN ratios were not shown in the previous study.

In conclusion, although the IGFR-1 is primarily synthesized by hepatocytes in a GH-dependent manner, the serum IGFR-1 levels were not associated with the serum levels of liver function tests in the healthy adults. In additional, the IGFR-1 is also produced by the bone and muscle and the interactions between bone and muscle were shown in the previous study. In this study, the IGFR-1 levels were positive and significant correlations with CK, ALP and BALP levels, but not with the urinary Dpd levels and Dpd/CRTN ratios. Therefore, the serum IGFR-1 levels associated with the bone formation markers, not the bone resorption markers under general physical activity in the healthy adults. Recently, IGFR-1 is a potential treatment in the patients with muscle atrophy. In clinical performance, the Duchenne muscular dystrophy patients received 6 months of recombinant human insulin-like growth factor-1 therapy improved linear growth. The physician needs to consider the effects of bone formation and muscle damage markers on the IGFR-1 levels in the management of IGFR-1-related disorders. The less sample size was our limitation. It is worthy to investigate the further studies by a large sample size in the future.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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