Evaluating the Fibroblast Growth Factor-23 and Phosphate in Iraqi Patients with Acromegaly

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Abstract

Fibroblast growth factors-23 (FGF-23) are a class of cell signaling proteins produced by macrophages. They have a range of roles, but they play a particularly important role in the development of animal cells, where they are essential for appropriate growth. Phosphate, which is found in the body as both organic and mineral phosphate, plays crucial roles in cell structure, communication, and metabolism. Most phosphate in the body resides in bone, teeth, and inside cells, with less than 1% circulating in serum. The aim of the study is to evaluate the levels of the Fibroblast Growth Factors-23 and phosphate and receiver operating characteristic (ROC) in acromegaly patients against healthy control. A case control study Fibroblast Growth Factors-23, Phosphate, Growth hormone and Insulin like growth factor-1 were carried out by recruiting 61 acromegalic patients who were enrolled in the study plus 60 control group. The results showed significant higher values in Fibroblast Growth Factors-23 and Phosphate levels in acromegalic patients than healthy control group whereas the Mean±S.D was (3627.49±395.77, 1809.94±159.63) and (1.44±0.58, 0.59±0.26) and we found the Fibroblast Growth Factors-23 was high in control group among men versus women (1866.81±177.86, 1756.98±121.07) and (P value 0.009). According to the current study, patients with acromegaly have high significant Fibroblast Growth Factors-23 and phosphate levels than the healthy control group and they are the most specific and sensitive marker in acromegalic patients in a term of defining and excluding the disease.

Keywords: Acromegaly, Fibroblast growth factors-23, Growth hormone, Insulin like growth factor-1, Phosphate.

Introduction

Acromegaly is characterized rare endocrine disease 1 by elevated levels of insulin like growth factor (IGF-I) and excess growth hormone (GH) concentrations 2-5. It is often brought on by a pituitary adenoma that secretes growth hormone, and middle-aged people are most frequently diagnosed with it 6-8. Excess GH is released into the blood by the adenoma, but IGF-I is mostly released by the liver when GH binds to hepatic GH receptors, which subsequently promotes systemic body development and metabolic processes 9-11. Acromegaly is linked to higher morbidity and death, primarily due to cardiovascular complications. There are several comorbidities, including sleep apnea syndrome at the top of the list, diabetes mellitus, arterial hypertension, and other respiratory issues 12-14. Therapy for acromegaly patients aims to reduce elevated levels of GH and/or IGF-I, however symptoms of the condition may linger despite pharmacologic treatment 15, 16. Although surgical excision is the chosen main treatment option, it is not always suitable and, depending on the size,
invasiveness, and expertise of the surgeon, only controls the illness in around half of patients. While there are currently many other alternatives for medical therapy, including dopamine agonists, growth hormone (GH) receptor antagonists, somatostatin analogs (SSA), and somatostatin receptor ligands (SRL). Fibroblast Growth Factors-23 (FGF-23) is a 32 kDa glycoprotein, it is essential for maintaining phosphate balance because of the effects they have on their target organs, such as the kidney and parathyroid gland. The FGF-23 is released into the bloodstream by osteoblasts and osteocytes, where it affects the kidney, parathyroid, heart, bone, and perhaps other organs. FGF-23 is a cardiovascular disease biomarker in those with chronic kidney disfunction. Even in healthy people, there is evidence that it is linked to decreased vasoreactivity and increased arterial stiffness. The FGF-23 may be best understood by identifying tumors where it is released in excess. Osteomalacia brought on by a tumor, which is similar to acromegaly, is an acquired condition following the removal of the tumor, which is the source of excessive FGF-23. The production of FGF-23 is induced by age, dietary phosphate overload, chronic kidney disease (CKD), and decreased glomerular filtration rate (GFR). Systemic phosphate regulation, which is a result of delicate endocrine feedback loops that affect the intestines, kidney, and skeleton, is essential for hydroxypapatite formation during bone mineralization. After an increase in blood phosphate or 1,25(OH)2 vitamin D (1, 25D), FGF-23 is created in bone and works with the kidney to reduce phosphate (PO4) reabsorption. Phosphate is critical for life, involved in a variety of cellular functions, including energy transfer, membrane biology, signal transduction, and endoskeleton organization. In humans, bones and teeth contain around 85% of the body's total phosphorus, with the remaining 15% contained in nucleic acids, cell membrane phospholipids, phospho-proteins, energy-rich molecules (such ATP), and inorganic phosphate (PO4) in blood. As IGF-1 enhances phosphate reabsorption in the proximal tubules by upregulating the sodium-phosphate transporters, hyperphosphatemia affects around 70% of individuals with acromegaly. In individuals with acromegaly, the blood phosphate content can be utilized as a marker for the disease's progression. The aim of the study is to evaluate the levels of the FGF-23 and PO4 and receiver operating characteristic (ROC) in acromegaly patients against healthy control.

Materials and Methods

Selection of Patients: This study was carried out in the National Diabetic Center for Treatment and Research/ Mustansiriya University in Baghdad/Iraq for the period from November 2022 to January 2023, after obtaining ethical consent from the review board and a verbal consent of participation from the subjects. The study included 121 subjects that suffer from acromegaly and healthy control group. They were divided into the groups:

1. Sixty one subjects suffering from Acromegaly (patients’ group) (35 males and 26 females)
2. Sixty (control group) (30 males and 30 females).

Inclusion Criteria: Patients acromegaly aged 30-65 years old.

Exclusion Criteria: Thyroid disease, heart and kidney disease, as well as pregnant women.

Sample Collection: The following parameters were measured of the study: FGF-23, PO4, GH and IGF-1 levels.

Results and discussion

Fibroblast growth factors-23 and phosphate levels were measured from serum samples by the enzyme-linked immunosorbent assay (ELISA) using kit (My Bio Source, USA and LINER, Spain), while growth hormone and insulin-like growth factor were measured (Diasorin, Italy) by the blood samples (5ml) were collected from acromegalic patients and healthy, then blood was centrifuged at 3000 rpm for 10 min. it was kept at a temperature of -20°C.

Statistical Analysis: The significance of the results was evaluated using SPSS (version 25.0, SPSS inc, Chicago, IL, USA). Summary data are presented as means ± SD. The statistical difference between continuous variables was analyzed using independent sample student’s t tests. Other tests used receiver operating characteristic ROC.
In table 1 FGF-23 is found to be 3627.49±395.77 in acromegalic patients and 1809.94±159.63 in the control group, the difference is highly significant (p <0.001). Phosphate is found to be high in patients group versus the healthy control, thus PO4 is 1.44±0.58 in patients and 0.59±0.26 in control group and the difference is highly significant (p < 0.001).

Growth hormone in acromegalic patients is 7.05±3.53 while in the control it is 0.70±0.29 and the difference is highly significant (p <0.001). Insulin like growth factor is 482.96±238.28 in patients and 105.28±6.5 in the healthy control, the difference is highly significant.

In table 2, the difference between men and women did not reach statistical significance among patients’ group so the P value is 0.600, 0.428, 0.378, and 0.839 for FGF-23, PO4, GH, and IGF-1 respectively. But in the control group FGF-23 is found to be high among men versus women (1866.81±177.86, 1756.98±121.07) and P value is found to be 0.009 while the difference in other variables is not significant P value is 0.390, 0.190, and 0.654 for PO4, GH, and IGF-1 respectively.

According to ROC curve, the area under the curve (AUC) for the FGF-23 is 1.000, and 95% CI with sensitivity and specificity are (100,100), p<0.001 respectively and the best cut–off point is found to be 2217 pg/ml. This means the test value higher than 2217 pg/ml is considered healthy condition whereas the value that is less than 2217 pg/ml represents the unusual case as shown in Fig 1.

Table 1. The baseline characteristics of the Acromegalic patients and Healthy control group counterparts

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Acromegaly</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>61</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Male/Female</td>
<td>35/26</td>
<td>30/30</td>
<td></td>
</tr>
<tr>
<td>FGF-23 (pg/ml)</td>
<td>3627.49±395.77</td>
<td>1809.94±159.63</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PO4 (mg/dL)</td>
<td>1.44±0.58</td>
<td>0.59±0.26</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GH (ng/ml)</td>
<td>7.05±3.53</td>
<td>0.70±0.29</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IGF-1(ng/ml)</td>
<td>482.96±238.28</td>
<td>105.28±6.5</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Table 2. The biochemical variables (FGF-23, PO4, GH, and IGF-1) in patients and control group according to their gender.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Acromegaly Mean±S.D</th>
<th>Healthy Control Mean±S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGF-23</td>
<td>Male 3651.24±356.21, Female 3592.96±453.75</td>
<td>Male 1866.81±177.86, Female 1756.98±121.07</td>
</tr>
<tr>
<td></td>
<td>P value 0.600</td>
<td>P value 0.009</td>
</tr>
<tr>
<td>PO4</td>
<td>Male 1.39±0.55, Female 1.51±0.61</td>
<td>Male 0.62±0.29, Female 0.56±0.24</td>
</tr>
<tr>
<td></td>
<td>P value 0.428</td>
<td>P value 0.390</td>
</tr>
<tr>
<td>GH</td>
<td>Male 7.40±3.65, Female 6.59±3.38</td>
<td>Male 0.62±0.19, Female 0.79±0.34</td>
</tr>
<tr>
<td></td>
<td>P value 0.378</td>
<td>P value 0.019</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Male 477.54±206.98, Female 490.26±279.11</td>
<td>Male 105.67±6.16, Female 104.90±6.99</td>
</tr>
<tr>
<td></td>
<td>P value 0.839</td>
<td>P value 0.654</td>
</tr>
</tbody>
</table>

Independent sample student t test, Data are expressed as mean±SD. p < 0.01: high significant.
Figure 1. ROC curve analysis of serum FGF-23 in patients against healthy control

According to ROC curve, the area under the curve (AUC) for the PO4 is 0.912, and 95% CI with Sensitivity and Specificity are 85.5, 81.7, p ≤ 0.001 respectively and the best cut–off point is found to be 0.728 ml/dl. That means the test value less than 0.728 ml/dl is considered healthy conditions whereas the value that is higher than 0.728 ml/dl represents the unusual case as shown in Fig 2.

Figure 2. ROC curve analysis of serum PO4 in patients against healthy

This study was conducted to find out the impact of FGF-23 and phosphate (PO4) on 61 patients with acromegaly and 60 with control group. The FGF23 is a crucial bone hormone that regulates the production of 1, 25(OH) 2D3 (calcitriol), active vitamin D, and parathyroid hormone (PTH), in addition to directly affecting renal phosphate transport. It is produced by a variety of cell types throughout fetal development, but in adults, the main cellular source is bone, which includes osteocytes, osteoblasts, and bone marrow. In the few studies, bone produced far more FGF23 protein than did other tissues, which suggests that bone serves as the primary source of circulating FGF23 in both health and sickness. TIO is one example, which is brought on by tumor cells producing excessive amounts of FGF23. The FGF23 is known to have a role in the control of phosphate balance in addition to having negative effects on cardiac function, the vasculature, inflammatory and immunological processes, and not only in patients with CKD but also in people in the general population. Endocrine, paracrine, and autocrine actions are produced by FGF-23. Increased arterial stiffness, total body atherosclerosis, LVH, and, ultimately, an increased risk of cardiovascular mortality are all linked to higher levels of FGF-23, even in individuals who do not have renal failure. Patients with acromegaly frequently have mild hyperphosphatemia as indicated by Yalin, G. Y., where GH increases tubular PO4 reabsorption through higher GFR levels, which has an excellent influence on serum PO4 levels. Previous research demonstrated that people with acromegaly who have high GH levels also have hyperphosphatemia and enhanced renal PO4 reabsorption. Long-term hypophosphatemia and a lack of 1, 25-dihydroxyvitamin D disrupt the process of bone mineralization, which leads to osteomalacia. Given that hyperphosphatemia has been linked to a rise in overall morbidity and mortality in the population monitoring for acromegaly may benefit by evaluating the impact of high PO4 levels, since it inhibits 1-hydroxylase in the proximal tubule. FGF-23 is a crucial hormonal regulator of calcitriol synthesis where higher calcitriol levels and improved dietary phosphate absorption are possible outcomes of low FGF-23. Indeed, a significant correlation between IGF1 and FGF23 was discovered, and patients with acromegaly had higher levels of FGF23. Therefore, IGF1 may have opposing effects on FGF23. Untreated acromegalic individuals had higher FGF-23 levels than those who had received treatment, according to a previous study. In contrast, all of our patients' FGF-23 levels were within the normal range prior to therapy.

Conclusion

According to the current study, FGF-23 and PO4 levels were higher significantly in patients with acromegaly than the healthy control group. The sensitivity and specificity for FGF-23 and PO4 were high in the patients group versus the healthy control.

Acknowledgment

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Author’s Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for republishing, which is attached to the manuscript.

Authors’ Contributions

Both author, S.A and A.SH, contributed to the design, implementation of the research, to the analysis of the results and to the writing of the manuscript, all authors discussed the results and commented on the manuscript.

References


Tقييم عوامل نمو الخلايا الليفية-23 والفسفات في المرضى العراقيين الذين يعانون من ضخامة الأطراف

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قسم الكيمياء، كلية العلوم للبنات، جامعة بغداد، بغداد، العراق.

الخلاصة

عوامل نمو الخلايا الليفية 23 هي أحد أصناف بروتينات الإشارات الخلوية تنتج بواسطة الخلايا البلعمية. لديها مدى واسع من الأدوار، لكنها تلعب دور مهم بشكل خاص في تطور الخلايا الحيوانية. حيث تكون ضرورية للنمو. يوجد الفوسفات في الجسم على شكل فوسفات عضوي ومعدني. ويلعب الفوسفات أدوار مهمة في تطوير الخلايا، والتواصل، والتمثيل الغذائي. معظم الفوسفات في الجسم في العظام والأسنان وداخل الخلايا حيث يتواجد أقل من 1% في مصل الدم. الهدف من الدراسة هو قياس مستويات عوامل نمو الخلايا الليفية -23، والفوسفات وهرمون النمو في مرضى ضخامة الأطراف مقابل مجموعة الأصحاء. تم أجراء دراسة عوامل نمو الخلايا الليفية -23، والفوسفات، وهرمون النمو، وعوامل النمو الشبيه للأنسولين -1 من قبل 61 مريضا. عوامل نمو الخلايا الليفية -23، والفوسفات، وهرمون النمو عالية في المجموعة الضابطة بين الرجال مقابل النساء. 0.6670. ووجدت الدراسة، أن المرضى الذين يعانون من ضخامة الأطراف لديهم عوامل نمو كبيرة للأورام الليفية -23، ومستويات الفوسفات مقابل مجموعة التحكم الصحية، وهي العلامة الأكثر تحديدا وحساسية في مرضى ضخامة الأطراف في مصطلح تعريف واستبعاد المرض.

الكلمات المفتاحية: ضخامة الأطراف, عامل نمو الخلايا الليفية (FGF-23), هرمون النمو (GH), الفوسفات (PO4), أورام النمو الشبيه للأنسولين-1 (IGF-1)