Significance of Measuring IGF-1 Levels in Adolescent Patients with Type 1 Diabetes Mellitus as a Prognostic Marker of Glycaemic and Lipid Profile Control

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ABSTRACT

The study aimed at evaluating the effect of elevated serum insulin-like growth factor-1 (IGF-1), which is a by-product of growth hormone in the body on glycaemic control (assessed by measuring HbA1c) and lipid profiles in adolescent patients (aged between 12 and 18 years) suffering from diabetes mellitus Type 1 (childhood onset diabetes mellitus). Thirty patients with diabetes mellitus type one were enrolled in the study within the age range mentioned (mean age was 15.2 ± 3). These patients had high-normal IGF-1 levels according to the normal standard range for their age group). A second group of thirty patients with diabetes mellitus type 1 with normal IGF-1 levels (mean age was 14.6 ± 2.5) were also enrolled for this study. A third group included thirty age and sex matched healthy controls. HbA1c was measured in all of the patients involved in the study as well as serum IGF-1. Lipid profiles were assessed and they included total cholesterol, low density lipoproteins (LDL) High density lipoproteins (HDL) and serum triglycerides. A significant elevation in HbA1c levels was observed in diabetes mellitus type 1 patients with normal levels of IGF-1 as compared to patients with diabetes mellitus type 1 with high normal IGF-1 levels or normal control subjects (mean HbA1c levels for group 2 as compared to groups 1 & 3 were 9.20 ± 0.64 vs. 7.01 ± 0.56 vs. 5.11 ± 0.57 respectively, p<0.01). A significant negative correlation was established between serum IGF levels and HbA1c (r=-0.46, p=0.02). These results required the reassessment of management protocols for patients belonging to Group 2. Serum total cholesterol levels, LDL-C, and triglycerides were significantly higher in the second group as compared to the other groups while HDL levels in the same group were found to be significantly lower. A significant negative correlation was established between serum LDL-C levels and IGF-1 levels measured in all participants (r=-0.41, p=0.02). This study concluded that elevation in IGF-1 levels (which is a good indicator of Growth hormone levels) in the body ) has its positive effects on glycaemic control and lipid profiles in adolescent patients receiving treatment for type 1 diabetes mellitus, therefore it is valuable as a prognostic tool for this disease.

Keywords: HbA1c, IGF-1, diabetes mellitus type 1, lipid profiles.

INTRODUCTION

Insulin-like growth factor 1 (IGF-1), also called somatomedinC, is a protein that, in humans, is encoded by the IGF1 gene. IGF-1 has also been denoted as a "sulfation factor" and its effects were named "non-suppressible insulin-like activity" (NSILA) in the 1970s.\(^1\)

IGF-1 is a hormone that is similar, in molecular structure, to insulin. A synthetic analog of IGF-1, mecamsermin is used for the treatment of growth failure.\(^2\) IGF-1 consists of 70 amino acids in a

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single chain with three intramolecular disulfide bridges. IGF-1 has a molecular weight of 7,649 daltons.\(^{(3)}\)

IGF-1 is produced primarily by the liver as an endocrine hormone as well as in target tissues in a paracrine/autocrine fashion. Production is stimulated by the growth hormone (GH) and can be retarded by under-nutrition, growth hormone insensitivity, lack of growth hormone receptors, or failures of the downstream signalling pathway post GH receptor including SHP2 and STAT5B. Approximately 98% of IGF-1 is always bound to one of 6 binding proteins (IGF-BP). IGFBP-3, the most abundant protein, accounts for 80% of all IGF binding. IGF-1 binds to IGFBP-3 in a 1:1 molar ratio. In rat experiments the amount of IGF-1 mRNA in the liver was positively associated with dietary casein and negatively associated with a protein-free diet.\(^{(4)}\)

The measurement of serum insulin-like growth factor-1 (IGF-1) is a useful screening test for acromegaly.\(^{(5)}\) The normal reference range for IGF-1 varies extensively, peaking during puberty and declining with progression of age.\(^{(6)}\) With the onset of puberty, the release of growth hormone (GH) is stimulated through sex steroids with estrogen being the main stimulator of GH release both in males and females.\(^{(7)}\) Although in males testosterone also stimulates the release of GH, the majority of the GH effect still occurs through aromatization of testosterone to estrogen.\(^{(8)}\) Once puberty has been completed, the levels of serum IGF-1 drop by fifty per cent during early adulthood and then continue to decline throughout adult life.\(^{(9)}\) Therefore, serum IGF-1 levels are interpreted against age and gender-specific reference ranges.

When subjects are well nourished, the GH-induced stimulation of IGF-1 and insulin is important for anabolic storage and growth of lean body mass (LBM), adipose tissue, and glycogen reserves. During fasting and other catabolic states, GH predominantly stimulates the release and oxidation of FFA, which leads to decreased glucose, and protein oxidation and preservation of LBM and glycogen stores. The most prominent metabolic effect of GH is a marked increase in lipolysis and FFA levels. In the basal state, the effects of GH on protein metabolism are modest and include increased protein synthesis and decreased breakdown at the whole body level and in muscle together with decreased amino acid degradation/oxidation and decreased hepatic urea formation. During fasting and stress, the effects of GH on protein metabolism become more pronounced; lack of GH during fasting increases protein loss and urea production rates by approximately 50%, with a similar increase in muscle protein breakdown. GH is also a counter-regulatory hormone that antagonizes the hepatic and peripheral effects of insulin on glucose metabolism via mechanisms involving the concomitant increase in FFA flux and uptake. This ability of GH to induce insulin resistance is significant for the defence against hypoglycemia, for the development of "stress" diabetes during fasting and inflammatory illness, and perhaps for the "Dawn" phenomenon (the increase in insulin requirements in the early morning hours). Adult patients with GH deficiency are insulin resistant—probably related to increased adiposity, reduced LBM, and impaired physical performance—which temporarily worsens when GH treatment is initiated.\(^{(9)}\)

**Aim of the Study**

This study aims at evaluating serum insulin like growth factor-1 (IGF-1) a by-product of growth hormone in the body as a prognostic marker of Glycaemic control (assessed by measuring HbA1c) and lipid profiles in a group of Egyptian adolescent patients (aged between 12 and 19 years) suffering from diabetes mellitus type 1 (childhood onset diabetes mellitus).

**Subjects and Methods**

**Subjects**

Participants in this study were selected from subjects attending the outpatient clinic at Kasr ElElny hospital, Cairo. Patient-informed detailed consent forms were completed by all patients before starting this work.
Thirty patients with diabetes mellitus type one with elevated IGF1 levels were enrolled in the study (15 males and 15 females) within the age range mentioned (mean age for this group was 15.2 ± 3). These patients had high normal IGF-1 levels according to the standard reference range for their age group (126-602ng/ml for males and 224-559ng/ml for females). Exclusion criteria comprised patients with any other associated hormonal or metabolic disorders that could interfere with the present study.

A second group of thirty patients (15 males and 15 females) with diabetes mellitus type 1 (mean age was 14.6 ± 2.5) with normal IGF-1 levels according to the standard reference levels for this age group were also enrolled for this study. Similar exclusion criteria to those used for group 1 selection were exercised while enrolling patients for group 2.

A third group included thirty age and sex matched healthy controls (mean age was 14.9 ± 4.2).

**Methods**

1-Participants were subjected to careful medical history taking and a detailed clinical examination as well as measuring fasting and after two hours postprandial blood sugar and other laboratory investigations such as serum urea and creatinine, uric acid, AST and ALT liver enzymes.

2-Glycosylated haemoglobin (HbA1-C) was measured in all subjects participating in this study using an ELISA technique.

3-IGF-1 was measured in all subjects using ELISA kits obtained from Mediagnost co., Germany.

4-Lipid profiles were assessed for all patients and controls and they included: total cholesterol (TC), high density lipoproteins (HDL) low density lipoproteins (LDL) and serum triglycerides (TG) using a calorimetric method.

5-Statistical analysis was carried out to determine the significance of IGF-1 as a prognostic marker of glycaemic and lipid profile control in Type 1 diabetes mellitus patients using Statistica v. 10 software, USA. One-way ANOVA test was used for comparing the various parameters measured in the three groups. P values ≤ 0.05 were considered significant while P values ≤ 0.01 were considered highly significant. Pearson’s correlation coefficient (r) was used to estimate the correlation between the parameters tested in this study.

**RESULTS**

Table (1): reveals a comparison of the mean HbA1c levels (± SD) obtained from all subjects enrolled in the three groups of the study.

<table>
<thead>
<tr>
<th>Group</th>
<th>I (DM &amp; High Normal IGF-1)</th>
<th>II (DM &amp; Normal IGF-1)</th>
<th>III (Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IGF-1 (ng/ml)</td>
<td>572.5 ±25.4</td>
<td>368.2±126.3</td>
<td>327.5±135.4</td>
</tr>
<tr>
<td>± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean HbA1c (%)</td>
<td>7.01 ±0.56</td>
<td>9.20±0.64</td>
<td>5.11±0.57</td>
</tr>
<tr>
<td>± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value(ANOVA)</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IGF-1= Insulin-Like Growth Factor Type One, HbA1c= Glycosylated Haemoglobin, SD=Standard Deviation, P=Probability
Figure 1 illustrates the negative correlation established between serum IGF-1 and HbA1c in the subjects enrolled in the three study groups ($r=-0.46$, $p=0.02$).

Table (2): reveals a comparison of the mean total cholesterol, LDL-C, HDL-C and TG levels ($\pm$ SD) obtained from all subjects enrolled in the three groups of the study.

<table>
<thead>
<tr>
<th>Group</th>
<th>I (DM &amp; High Normal IGF-1)</th>
<th>II (DM &amp; Normal IGF-1)</th>
<th>III (Control)</th>
<th>P Value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/100 ml)</td>
<td>166±7.2</td>
<td>212±14.3</td>
<td>150±3.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LDL-C (mg/100 ml)</td>
<td>98±4.5</td>
<td>115±3.4</td>
<td>89±3.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-C (mg/100 ml)</td>
<td>64±5.2</td>
<td>34.3±4.2</td>
<td>55±4.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TG (mg/100 ml)</td>
<td>133±2.9</td>
<td>217±2.6</td>
<td>99±3.7</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table (3): reveals the Pearson’s correlation coefficient ($r$) for the lipid profile parameters measured in all participating groups against their corresponding IGF-1 levels.

| Correlation of Lipid Profile Parameters with IGF-1 Levels in all Study Groups ($r$) |
|----------------------------------|---------------------------------|-------------------|-----------------|-----------------|
| TC                               | -0.38 (p=0.03)                  |                   |                 |                 |
| LDL-C                            | -0.41 (p=0.02)                  |                   |                 |                 |
| HDL-C                            | 0.36 (p=0.03)                   |                   |                 |                 |
| TG                               | -0.34 (p=0.03)                  |                   |                 |                 |

Figure 2 illustrates the negative correlation demonstrated between serum IGF-1 and LDL-C levels in the subjects enrolled in the three study groups ($r=-0.41$, $p=0.02$).

Fig. (2): Correlation between LDL-C and IGF-1 in Adolescents with Type 1 DM.
DISCUSSION

Insulin-like growth factor 1 (IGF-1) is a hormone, similar in its structure, to insulin that plays an important role in childhood growth and has anabolic effects in adults, as it is involved in the regulation of growth and cellular proliferation\(^{(11)}\). In glucose metabolism, a lower than normal IGF-1 was shown to be related to insulinopenia, as IGF-1 is part of a complex feedback loop at the level of the hypothalamus and/or pituitary. Therefore, low values of IGF-1 lead to higher insulin resistance through growth hormone hypersecretion that is one of the anti-insulin hormones\(^{(12)}\).

In the current study, a significant elevation in HbA1c levels was observed in diabetes mellitus type 1 patients with both normal levels of IGF-1 as compared to patients with diabetes mellitus type 1 and high normalIGF-1 levels or normal control subjects (mean HbA1c levels were 9.20±0.64 vs. 7.01 ±0.56 vs. 5.11 ±0.57 respectively, p<0.01). A significant negative correlation between IGF-1 and HbA1c levels was also observed in all three study groups (r= -0.46, p=0.02).

These results were found to be in concordance with the results obtained by Faerch and his co-workers (2012)\(^{(13)}\) who found that diabetes mellitus type 1 patients with poor glycaemic control had lower serum IGF-1 levels as compared to those noted in well controlled patients. A negative correlation between IGF-1 and HbA1c levels was also established in the latter study. Another study by Palta and his co-workers (2014) found a positive effect of higher levels of IGF-1 on glycemic control in type 1 diabetes mellitus patients and demonstrated the same negative correlation mentioned earlier.\(^{(14)}\) On the other hand the results obtained in the current study were contradictory to those obtained by other authors including a study by Abdel Raheem and his co-workers (2013) who found that higher IGF-1 levels had a negative effect on glycemic control.\(^{(15)}\) These conflicting results could be attributed to differences in experimental design and patients’ age selection or exclusion criteria used in the latter study.

The elevation of HbA1c levels in diabetic patients with lower IGF-1 levels necessitated the re-categorisation and re-assessment of clinical management protocols to be carried out for patients belonging to Group 2.

Serum total cholesterol levels, Serum LDL-C and triglycerides were also found to be significantly higher in the second group as compared to the other two groups. On the other hand, HDL-C levels in Group 2 were found to be significantly lower (p<0.01 for all lipid profile parameters measured in the three groups).

Additionally, a significant negative correlation similar to that observed between serum HbA1c and IGF-1 levels was demonstrated for serum TC, LDL-C and TG levels in all participants (r= -0.38, -0.41 & -0.34 respectively) while serum HDL-C levels showed a significant positive correlation with IGF-1 levels (r=0.36).

A recent study by Kim and Lee (2014) established similar results to the current study and concluded that higher levels of circulating IGF-1 had a positive effect on lipid profile control in patients with type 1 diabetes mellitus thus lowering their risk of developing cardiovascular complications\(^{(16)}\). Their study demonstrated a negative correlation between TC, LDL-C and IGF-1 levels in diabetic adolescents and therefore higher serum IGF-1 levels carry a good prognostic value for such patients.

CONCLUSION

An elevation in IGF-1 levels (that in turn is a good indicator of growth hormone levels in the body) has a positive effect on glycaemic control in addition to its positive effect on lipid profiles in adolescent patients who are receiving treatment for type 1 diabetes mellitus and can be utilized as a valuable prognostic marker to adjust their management protocols.
REFERENCES


