Effect of 12 Months of Recombinant Human Growth Hormone Replacement Therapy on Insulin Sensitivity in GH-Deficient Adults as Determined by Different Methods

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Abstract:
BACKGROUND: Controversial results have been obtained in measuring insulin sensitivity (SI) during recombinant human growth hormone (rhGH) treatment in adult growth hormone deficient (GH-deficient) patients. AIMS: The aim of our study was to estimate SI before and during treatment using three different methods for quantifying insulin sensitivity in GH-deficient adults treated with rhGH. SETTINGS AND DESIGN: Twenty-one GH-deficient adults were treated with rhGH during 12 months. SI was estimated using Minimal model analysis, Homeostatic Model of Assessment (HOMA) and Quantitative Insulin Sensitivity Check Index (QUICKI) before and after 3, 6, 9 and 12 months of rhGH therapy. PATIENTS AND METHODS: Oral Glucose Tolerance Test (OGTT) and Frequently Sampled Intravenous Glucose Tolerance Test (FSIGT) were performed in each patient at respective time intervals. QUICKI and HOMA were calculated using basal values of glucose and insulin from FSIGT. Minimal model computer analysis was calculated from glucose and insulin data obtained during FSIGT. STATISTICAL ANALYSIS: Area under the curve for glucose, insulin and C-peptide were calculated using trapezoidal rule from OGTT data. Differences and correlations were tested using ANOVA for repeated measures, Wilcoxon's matched-paired test, paired t-test, Pearson's correlation and Bland Altman plot. RESULTS: There were no significant changes in SI using Minimal model analysis and QUICKI during rhGH treatment. On the contrary, HOMA analysis indicated significant deterioration in SI after 12 months of therapy. CONCLUSION: Our study did not demonstrate any changes in SI using Minimal model and QUICKI analysis, while there was significant increase in insulin resistance using HOMA model. We suggest that the choice of method for the determination of SI may influence the interpretation of results concerning the effect of rhGH therapy on SI in GH-deficient adults. (J Postgrad Med 2002;48:260-265)

Key Words: Insulin sensitivity, GH-deficient adults, rhGH treatment

There are contrasting reports concerning the effect of recombinant human growth hormone (rhGH) replacement therapy on glucose metabolism. Some studies have reported obvious deterioration of insulin sensitivity (SI) with concomitant elevation of basal and stimulated glucose and insulin levels.1,2 Changes in the kinetics of insulin and C-peptide have also been noted.3 There are others who have not found any significant change in SI in comparison with pretreatment values.4, 5 Different methods used for the estimation of SI and variable pretreatment characteristics of GH-deficient patients that were included in the studies could account for these differences.

Euglycaemic hyper-insulinaemic clamp is considered as the “gold standard” for quantifying SI in vivo, but this method has procedure-related practical limitations in clinical investigations.5 Introduction of Minimal model analysis, Homeostatic Model of Assessment (HOMA) and Quantitative Insulin Sensitivity Check Index (QUICKI) for determination of SI and/or insulin resistance permitted the investigation of larger number of patients. Relatively simple investigational procedure is the chief attribute of these methods.7 It was recently shown that measures of SI is inversely related to resistance and it was suggested that correlations should be examined among sensitivities or among resistance measurements. The most straightforward comparison between a different index of SI and the HOMA index, which is a measure of insulin resistance, is obtained by first inverting it so that it is also expressed as a sensitivity.7 Therefore, we decided to evaluate the effect of rhGH replacement therapy on peripheral SI and/or insulin resistance during the twelve months course of rhGH therapy in a group of adult patients with hypopituitarism using three different methods for its determination - Minimal model analysis (MINMOD), QUICKI and HOMA.
Patients and Methods

Twenty-one GH-deficient patients participated in 12 months rhGH (Norditropin, Novo Nordisk A/S) replacement therapy study. GH-deficiency was defined as GH peak level being less than 3 μg/l after insulin-induced hypoglycaemia. All study subjects were adequately treated with hydrocortisone, testosterone and/or L-thyroxin, if necessary, for at least one year before initiation of rhGH therapy. The local Ethics committee approved the study, and all patients were informed about the possible side effects and their consent was obtained prior to enrolment. The dose titration for rhGH was adjusted in order to achieve the mean value for normal IGF-I range (normal: 15 – 35 nmol/l). Mean rhGH dose was 26.8±3.2 nmol/l. In two female patients the dose of rhGH was reduced to 1 IU/day due to the side effects of therapy. A control group was titrated for rhGH was adjusted in order to achieve the mean value for normal IGF-I range (normal: 15 – 35 nmol/l). Mean rhGH dose was 0.75

Side effects and their consent was obtained prior to enrolment. The dose

Table 1: Changes in $S_i$ (10$^{-3}$ min$^{-1}$/[(mIU/l)] basal insulin (mIU/l), $AIR_{0-8}$ (mIU/l x min) and $S_{IGF-I}$ (10$^{-3}$ min$^{-1}$) values during rhGH therapy using Minimal model analysis.

<table>
<thead>
<tr>
<th>$S_i$</th>
<th>Insulin</th>
<th>$AIR_{0-8}$</th>
<th>$S_{IGF-I}$</th>
<th>0 month</th>
<th>0.06±0.37</th>
<th>17.60±54.44</th>
<th>603.66±157.18</th>
<th>2.67±0.34</th>
<th>8.21±5.9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>III month</td>
<td>1.99±0.35</td>
<td>19.77±3.2</td>
<td>617.56±126.7</td>
<td>2.47±0.22</td>
<td>24.2±2.9</td>
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<tr>
<td></td>
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<td>VI month</td>
<td>3.24±0.43</td>
<td>13.43±0.96</td>
<td>588.79±82.94</td>
<td>2.18±0.23</td>
<td>25.3±3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IX month</td>
<td>4.29±1.15</td>
<td>15.86±2.53</td>
<td>688.71±155.51</td>
<td>2.70±0.70</td>
<td>23.3±2.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>XII month</td>
<td>2.73±0.54</td>
<td>14.99±1.93</td>
<td>688.71±155.51</td>
<td>2.30±0.32</td>
<td>23.3±2.8</td>
</tr>
</tbody>
</table>

$P$ value is representative for any time intervals, except for $IGF-I$ values before and after initiation of rhGH therapy (marked with *).


Mitic D et al: Effect of Growth Hormone Replacement on Insulin Sensitivity
Our data suggests that rhGH therapy in GH-deficient (GHD) adults decreases SI in this group of patients. The HOMA analysis, before and after therapy, clearly indicates a significant decrease of SI. On the contrary, MINMOD and QUICKI analysis demonstrated non-significant decrease in SI. This is most likely due to a small sample size. Changes in AUC for glucose and insulin sensitivity were also observed. The results obtained by Bland Altman plot suggest comparability between MINMOD and HOMA as methods for quantification of insulin sensitivity, so the differences obtained using these tests are probably due to a small sample size. The AUC for glucose and insulin during OGTT were significantly increased before and after rhGH therapy.

Discussion

Our data suggests that rhGH therapy in GH-deficient (GHD) adults decreases SI in this group of patients. HOMA analysis, before and after therapy, clearly indicates a significant decrease of SI. On the contrary, MINMOD and QUICKI analysis demonstrated non-significant decrease in SI. This is most likely due to a small sample size. Changes in AUC for glucose and insulin sensitivity were also observed. The results obtained by Bland Altman plot suggest comparability between MINMOD and HOMA as methods for quantification of insulin sensitivity, so the differences obtained using these tests are probably due to a small sample size. The AUC for glucose and insulin during OGTT were significantly increased before and after rhGH therapy.

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lin before and after therapy, suggests an increase in insulin resistance, as confirmed by the HOMA index. One patient without familial predisposition for diabetes mellitus developed impaired glucose tolerance (IGT) after therapy in absence of change in the BMI. Similar results were obtained during other studies, with exceptions in the percentage of patients who developed IGT. Others authors did not find a change in glucose tolerance after 6 months of rhGH therapy. It is postulated that the observed difference amongst studies may be due to a difference in number of patients enrolled and/or dif-
ferences in pretreatment characteristics of patients, particularly those who are susceptible to develop IGT or diabetes. It was also suggested that only children susceptible to develop diabetes mellitus, before initiation of rhGH therapy, are at a greater risk to develop IGT or diabetes during therapy course. The existence of insulin resistance and its consequences in GHD adults before the initiation of the rhGH therapy was observed in several studies. It was shown that this group of patients had normal fasting levels of glucose, insulin, C-peptide and free fatty acids.

It was suggested that insulin resistance in GHD patients is generated due to severe inhibition of insulin-stimulated glycogen synthase (GlySyn) activity, accompanied by a reduced baseline glycogen content, low-to-normal glucose 6-phosphate (G6P) levels and high total intracellular glucose concentrations in the presence of persisting euglycaemia. These abnormalities are not present in other insulin resistant states associated with reduced insulin-stimulated GlySyn activity (i.e. obesity, diabetes mellitus type 2).

Controversial results in measuring $S_I$ during rhGH treatment were obtained in a number of studies.

An initial deterioration of $S_I$ during the course of rhGH therapy was observed in most studies, as we observed in our study. However, both glucose and insulin levels have a tendency to return to pre-treatment values during continuation of rhGH treatment. A persistent deterioration of $S_I$ during and after rhGH therapy was demonstrated using euglycaemic hyper-insulinaemic clamp as a method for assessment of $S_I$. Index of insulin resistance after 12-months of rhGH therapy remains unchanged using HOMA.

In two long-term controlled studies, there was no significant difference in $S_I$ before and after rhGH therapy in GHD adults, or between rhGH treated and non-treated GHD adults, as well as between rhGH-treated GHD adults and healthy controls. Our study also did not demonstrate any significant difference in insulin sensitivity ($S_I$) using MINMOD and QUICKI index.

Recently, Katz et al suggested QUICKI as the most relevant substitution for hyper-insulinaemic euglycaemic clamp in estimation of $S_I$. HOMA represents a structural computer model of the glucose/insulin feedback system for the estimation of insulin resistance. Both QUICKI and HOMA methods use only basal concentrations of glucose and insulin for estimation of $S_I$. Increased glomerular filtration rate and renal blood flow during rhGH therapy may alter clearance of insulin and C-peptide. Therefore, actual concentrations of insulin and C-peptide underestimate the increase in insulin secretion during rhGH treatment, limiting their role in calculation of index of $S_I$. MINMOD is more convenient procedure than the euglycaemic hyper-insulinaemic clamp and it appears that MINMOD may be the most convenient method for estimation of $S_I$ in GHD adults on the rhGH replacement therapy.

The use of different methods for determination of $S_I$ could contribute to the observed polarisation in $S_I$ results and may influence the degree of significance of deterioration of $S_I$ during rhGH replacement therapy. Discrepant results concerning $S_I$ in different studies may reflect differential rhGH dose titration, preexisting $S_I$, the age of studied patients, and according to our experience in this study, different methods used for the assessment of $S_I$.

In conclusion, our results indicate that the choice of method used for quantification of $S_I$ could influence conclusion concerning the effect of rhGH on $S_I$. MINMOD and QUICKI index did not demonstrate any significant difference in $S_I$ in adult growth hormone deficient patients before and after the 12 month therapy with rhGH, while HOMA index indicated a significant increase in insulin resistance. This difference could be accounted for due to a small sample size. Observed differences in the results between the different methodologies may limit the comparisons between groups that used different method for quantification of $S_I$ and could contribute to observed controversial results of the effect of rhGH therapy on $S_I$.

Acknowledgements
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References
Very important to determine the role of GH therapy both for growth hormone deficient adults as well as a potential therapy for conditions such as metabolic syndrome with associated obesity.

Micic et al here describe a study in which they have administered rhGH to 21 GHD adults and studied the effect on insulin sensitivity in these patients. To their credit they compared three well-established techniques, the minimal model, the insulin sensitivity, and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. Comput Methods Programs Biomed 1986; 23:113-22.

Thus our decisions to use GH for different conditions and the potential side-effects such as increased insulin resistance and diabetes will await further studies, which hopefully will have larger sample size and use consistent study methods as the authors of this study strongly suggest.

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