Estimation of growth hormone secretion rate: impact of kinetic assumptions intrinsic to the analytical approach

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Langendonk, Janneke G., Johannes D. Veldhuis, Jacobus Burgragraaf, Rik C. Schoemaker, Adam F. Cohen, A. Edo Meinders, and Hanno Pijl. Estimation of growth hormone secretion rate: impact of kinetic assumptions intrinsic to the analytical approach. Am J Physiol Regulatory Integrative Comp Physiol 280: R225–R232, 2001.—We compared four common mathematical techniques to determine daily endogenous growth hormone (GH) secretion rates from diurnal plasma GH concentration profiles in 24 women (16 upper- or lower-body obese and 8 normal-weight individuals). Two forms of deconvolution analysis and two techniques based on a priori determined GH clearance estimates were employed. Deconvolution analyses revealed significant differences in the 24-h GH secretion rate between normal-weight and upper-body obese women, whereas the other two techniques did not. Moreover, deconvolution analyses predicted that the reduction in mean plasma GH concentrations in upper-body obese women was accounted for by impaired GH secretion, whereas the other methods suggested that obesity increases GH metabolic clearance. Thus we infer that disparate conclusions concerning GH secretion can be drawn from the same primary data set. The different inferences likely reflect dissimilar kinetic assumptions and the particular limitations intrinsic to each analytical approach. Accordingly, we urge caution in the facile comparison of calculated GH secretion data in humans, especially when kinetic and secretion measurements are performed under different conditions. The most appropriate way to determine the GH secretion rate in humans must be balanced by the exact intent of the experiment and the acceptability of different assumptions in that context.

human obesity

AT ANY GIVEN TIME, THE CONCENTRATION of growth hormone (or any other hormone) in plasma is the result of prior and ongoing secretion, distribution, and irreversible elimination. Reduced pituitary growth hormone (GH) secretion as a proximate cause of lower plasma GH concentrations reflects mechanisms that are fundamentally different from those subserving suppressed plasma GH levels in the face of increased secretion (e.g., as a result of a larger GH distribution volume and/or accentuated clearance). Thus to appreciate the cause and pathophysiological impact of hyposomatotropism, it is crucial to delineate the causal kinetic mechanisms.

The mean and integrated values [area under the curve (AUC)] of 24-h plasma GH concentration profiles provide an indirect measure of daily GH secretion. Indeed, because the volume of distribution (Vd) and clearance rate of GH exert conjoint effects on the plasma GH concentration, blood GH concentrations per se do not reliably reflect the GH secretion rate. Thus various analytical techniques have been developed to appraise GH kinetics in humans. For example, computer-assisted deconvolution analysis of frequently sampled plasma hormone concentrations is used widely. A secretory waveform-specific deconvolution technique can be employed to estimate daily (pulsatile) hormone secretion and the hormone half-life simultaneously from plasma concentrations measured serially over time (28). Waveform-independent nonparametric deconvolution methods have also been designed to estimate hormone secretion rates (31). The latter class of techniques requires a priori knowledge of hormone-elimination kinetics (i.e., a nominal plasma GH half-life). A third approach to map daily GH secretion employs the multiplication of individually determined (exogenous) GH clearance rates by the integrated (endogenous) 24-h serum GH concentration (26). GH clearance can be estimated in various ways, including by an analysis of the serum GH decay curves after a bolus injection (10, 24) or by steady-state infusion (4, 21, 31) of homologous GH. Alternatively, one can approximate clearance based on a nominal plasma half-life and body weight-dependent distribution volume for the hormone (9).

Plasma GH concentrations are known to be significantly reduced in obese individuals (11, 19, 30). Most of the foregoing strategies have been applied to determine GH secretion in obese humans (for example, see
Subjects and Study Design

Subjects

Sixteen obese and eight NW healthy premenopausal women were asked to participate through advertisements in local newspapers (for subject characteristics; see Table 2). The obese women were either identified as LBO or UBO on the basis of their waist-to-hip circumference ratio (LBO <0.81, and UBO >0.89). Any endocrine or other significant disease was excluded by medical history, physical examination, and biochemical screening. None of the subjects used oral contraceptives. Written informed consent was obtained from all subjects. The study was approved by the Ethics Committee of Leiden University Medical Center.

Study Design and Protocol

The study was designed as an open observational experiment and performed as part of a large project in which various hormone profiles were studied. The complete details of the protocol are described elsewhere (17). Briefly, plasma GH concentrations were determined at 10-min intervals for a full 24 h during the early follicular phase of the menstrual cycle. On a separate day, the metabolic clearance of exogenous GH and its distribution volume were estimated by analysis of the plasma GH decay curve after a 5-min infusion of 100 mU human recombinant 22-kDa GH, whereas endogenous GH secretion was suppressed by simultaneous somatostatin infusion (0.83 µg·min⁻¹·m⁻² body surface area). A two-compartment open-elimination model with a constant coefficient of variation residual error was used. Individual parameter estimates were obtained using nonlinear mixed effect modeling version IV software (NONMEM Project Group, Univ. of California, San Francisco, CA) for individual nonlinear least-squares curve fitting for each subject/occasion (23). Basal values (before 5-min GH infusion) were accounted for by modeling a variable steady-state infusion parameter ending at the time of recombinant human GH (rhGH) administration.

Methods to Assess the Daily Pituitary GH Secretion Rate

Method I. Deconvolution analysis. The joint effects of GH secretion and irreversible elimination on the resulting GH plasma concentration can be described by a convolution integral. The reverse process, back calculating the contributing secretion and elimination processes from the GH concentration profile, is called deconvolution analysis.

Method IA. Secretory Waveform-Specific Deconvolution. This model assumes that GH release from the pituitary gland takes place as a discrete finite series of bursts that can be approximated algebraically by a Gaussian-shaped or minimally skewed distribution of secretory rates of nonzero amplitude. In its simplest form, the convolution process is described by the following equation: C(t) = ∫₀¹ S(t)E(t-z)dz, where C(t) is the concentration of GH at time t, S(t) is the secretion function at time t, and E(t-z) is the elimination function, which describes the amount of hormone eliminated per unit distribution volume over the time interval (t-z).

Any given GH pulse is thus described by its location in time, amplitude, and half duration, as superimposed on a finite (0 or positive) basal (time invariant) GH secretory rate. The integral of each secretory burst yields the pulse mass. Computer-assisted deconvolution can estimate basal and pulsatile (and total) daily GH secretion as well as the apparent endogenous GH half-life. Because deconvolution analysis of endogenous hormone time series does not allow determination of hormone-distribution volumes, the deconvolution-derived GH secretion rate is expressed per liter of Vd.

Total daily (pulsatile + basal) GH secretion is reported. A detailed mathematical description of the above waveform-specific deconvolution method has been given elsewhere (31). The primary intrinsic kinetic assumptions and limitations of waveform-specific deconvolution analysis are summarized in Table 1.

Method IB. Secretory Waveform-Independent Deconvolution. This technique is designed to estimate hormone secretion rates without assuming any specific secretory waveform including the presence or absence of pulsatility. However, it requires a priori knowledge of hormone elimination rate constants or half-lives. The concentration of a hormone at any particular time is defined as the sum of the amount of hormone secreted at each previous time corrected for the amount of hormone eliminated between the time at which it was secreted and the time at which its concentration is observed. A general formula that describes the plasma GH concentration at any given time t in relation to all n samples observed before and at time t in this model is given by: C(t) = ∑ₙsᵢΔT·elim(t-Tᵢ), where sᵢ is the sample hormone secretory rate (mass·unit distribution volume⁻¹·unit time⁻¹) associated with the ith data point, ΔT is the time interval between successive data points, and elim is a function that describes GH elimination from plasma (31).

The initial (positive) estimates for the n secretory rates are found using Gold’s ratio-deconvolution method. Subsequently, each sample secretory rate is calculated by an iterative nonlinear least-squares parameter estimation algorithm to compute maximum likelihood sample secretory rates. During this process, the concentration-dependent within-assay variances associated with each sample mean are used in an
inverse weighing function. Total hormone secretion per day is calculated as the product of the mean (per min) secretory rate and the duration of the sampling interval. A detailed mathematical description of the above waveform-independent deconvolution method has been given elsewhere (12, 29, 31).

For waveform-independent estimates of GH secretion, the hormone-specific elimination process was described by a biexponential model with a mean first component half-life of 3.5 min, a second component half-life of 21 min, and a relative contribution of the slow component to the total elimination of 0.63. These values were based on reported endogenous GH decay after successive intravenous GH releasing hormone injections (5) and assumed for this analysis to be similar in the three groups. The primary intrinsic kinetic assumptions and limitations of waveform-independent deconvolution analysis are summarized in Table 1.

**Method II. Integrated plasma GH concentrations and exogenous clearance estimates.** This method estimates the total amount of GH secretion over 24 h on the basis of the AUC of the 24-h endogenous plasma GH concentration (determined by the trapezoidal rule) and individually determined exogenous GH clearance values, according to the following formula: daily GH secretion (mU) = clearance (l/min) x AUC (mU x l x −1 x min−1) (26). The primary intrinsic kinetic assumptions and limitations of this method are summarized in Table 1.

**Method III. Integrated plasma GH concentrations and nominal body weight-based kinetics.** In this model, the GH Vd is assumed to be 7% of total body weight (20), and GH half-life is assumed to be 23.5 min (15). Clearance is then calculated as: clearance (l/min) = (ln2/ t½) x Vd (9). Subsequently, daily GH secretion is estimated as in method II (above). The primary intrinsic kinetic assumptions and limitations of this method are summarized in Table 1.

**Growth Hormone Assay**

Plasma human GH concentrations were determined with an ultrasensitive 22-kDa specific immunofluorometric assay (Delfia hGH kit, Wallac Oy, Turku, Finland). The detection limit was 0.03 mU/l or 0.012 mg/l. The intra-assay coefficients of variation ranged from 1.6 to 8.4% over the GH concentration range of 50 to 0.25 mU/l.

**Statistical Analysis**

Because the distribution of data was skewed, they were natural-log transformed for statistical analysis. One-way analysis of variance and post hoc Bonferroni’s test for multiple comparisons were performed to detect differences among groups. Significance level was set at 5%. All results are presented as the means ± SD, unless otherwise indicated. Correlations between parameters were calculated using Pearson’s correlation coefficient. Calculations were performed using SPSS for Windows (v7.5.2; SPSS, Chicago, IL).

**RESULTS**

One subject in the LBO group was excluded from analysis, because values of all GH variables were far out of the normal range.

**Serum GH Concentrations Over 24 h**

The time-integrated mean 24-h serum GH concentration (AUC) was significantly lower in both groups
of obese women compared with their NW controls (Table 2).

**GH Secretion Rates**

**Method IA. Waveform-specific deconvolution analysis.** The total daily GH secretion rate (pulsatile + basal) per liter \( V_d \), as estimated by waveform-specific deconvolution analysis, was significantly lower in UBO women compared with NW controls, whereas LBO women appeared to have intermediate values (not significantly different from either NW or UBO values; Table 3). Estimated endogenous GH half-lives were similar in obese and NW women.

**Method IB. Waveform-independent deconvolution analysis.** Waveform-independent analysis of 24-h GH profiles predicted total daily GH secretion rates that were similar to those obtained by waveform-specific analysis. Accordingly, a significant difference in daily GH secretion rate per liter \( V_d \) was observed between UBO and NW women, whereas LBO women appeared to have intermediate values (not significantly different from either NW or UBO values; Table 3).

**Method II. Integrated plasma GH concentrations and exogenous clearance estimates.** Daily GH secretion was not different among groups when analyzed by AUC and exogenous GH clearance estimates. When daily GH secretion was normalized per liter of \( V_d \) (estimated by exogenous infusion), the differences among groups remained insignificant. However, GH clearance was increased significantly by \(~30\%) in obese compared with NW women. GH \( V_d \) as determined by analysis of the exogenous plasma GH decay curve, was not different between obese and NW women. Moreover, there was no correlation between GH \( V_d \) and body weight (Fig. 1).

**Method III. Integrated plasma GH concentrations and nominal body weight-based kinetics.** Daily GH secretion did not differ among the two obese groups and NW women when calculated by this method.

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### Table 2. Subject characteristics and integrated plasma GH concentrations

<table>
<thead>
<tr>
<th></th>
<th>NW</th>
<th>LBO</th>
<th>UBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>8</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Age, yr</td>
<td>38 ± 8</td>
<td>35 ± 5</td>
<td>38 ± 8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.4 ± 2.1</td>
<td>33.8 ± 4.4*</td>
<td>33.9 ± 3.1*</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.77 ± 0.04</td>
<td>0.76 ± 0.03</td>
<td>0.96 ± 0.05*†</td>
</tr>
<tr>
<td>GH-AUC 0–24 h, U·l⁻¹·min⁻¹</td>
<td>5.2 ± 2.5</td>
<td>2.6 ± 1.6*</td>
<td>2.4 ± 2.1*</td>
</tr>
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</table>

Data are presented as the mean ± SD. NW, normal-weight women; LBO, lower-body obese women; UBO, upper-body obese women. BMI, body mass index; AUC, area under the curve; GH, growth hormone. *Statistically significant difference compared with NW. †Statistically significant difference compared with LBO.

### Table 3. Estimated daily GH secretion rates and kinetic features

<table>
<thead>
<tr>
<th></th>
<th>NW</th>
<th>LBO</th>
<th>UBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily GH secretion/l ( V_d ), mU·day⁻¹·l ( V_d )⁻¹</td>
<td>218 ± 115</td>
<td>113 ± 72</td>
<td>84 ± 54*</td>
</tr>
<tr>
<td>GH half-life, min</td>
<td>15.6 ± 2.4</td>
<td>15.5 ± 1.3</td>
<td>15.6 ± 2.0</td>
</tr>
</tbody>
</table>

**Method IA. Waveform-specific deconvolution derived parameters**

**Method IB. Waveform-independent deconvolution derived parameters**

**Daily GH secretion/l \( V_d \), mU·day⁻¹·l \( V_d \)⁻¹ | 228 ± 121 | 97 ± 57 | 84 ± 82* |

**Method II. Integrated plasma GH concentrations and exogenous clearance estimates**

**Daily GH secretion, mU/day | 2,444 ± 1,345 | 1,911 ± 1,371 | 1,483 ± 1,248 |
| Daily GH secretion/l \( V_d \), mU·day⁻¹·l \( V_d \)⁻¹ | 229 ± 132 | 140 ± 79 | 132 ± 129 |
| GH clearance, ml/min | 470 ± 105 | 685 ± 138* | 619 ± 126* |
| GH distribution volume, l | 10.8 ± 1.9 | 12.5 ± 3.1 | 12.6 ± 3.9 |

**Method III. Integrated plasma GH concentrations and nominal body weight-based kinetics**

**Daily GH secretion, mU/day | 699 ± 341 | 724 ± 390 | 443 ± 446 |
| Daily GH secretion/l \( V_d \), mU·day⁻¹·l \( V_d \)⁻¹ | 154 ± 74 | 106 ± 54 | 70 ± 76 |
| GH clearance, ml/min | 135 ± 16 | 198 ± 28* | 194 ± 17* |
| GH distribution volume, l | 4.6 ± 0.5 | 6.7 ± 1.0* | 8.6 ± 0.6* |

Values are means ± SD. \( V_d \), volume of distribution. *Statistically significant difference compared with NW.
Obviously, GH distribution volume and clearance rate differed significantly between obese and NW women, because the analytical approach assumes these kinetic parameters to be directly dependent on body weight.

Correlations and comparison of results obtained by different methods. Although GH secretion estimates were strongly correlated among methods (Fig. 2), the absolute values obtained by the various techniques differed considerably (Table 3). Despite the differences in absolute values obtained by different methods, certain statistically significant differences among study groups were maintained, whereas others were not (Table 3).

GH secretion rates per liter $V_d$, determined by waveform-specific and waveform-independent techniques, were similar and strongly correlated (Table 3, Fig. 2).

In NW women, the GH secretion rates estimated by method II were similar to those estimated by deconvolution analysis. However, in obese women, the GH secretion rate normalized per liter $V_d$ determined by method II was $\sim 50\%$ greater than that derived by deconvolution analysis (Table 3, $P < 0.05$ for both deconvolution techniques in UBO and LBO).

Clearance values and distribution volumes estimated on the basis of body weight (method III) were considerably lower than those determined by exogenous GH administration (method II, $P < 0.05$ for all groups). Therefore, total daily GH secretion ($P < 0.05$ for all groups) and GH secretion per liter $V_d$ ($P < 0.05$ for NW and UBO subjects only) calculated by method III were considerably lower than GH secretion rates derived from method II (Table 3).

GH secretion rates per liter $V_d$ derived from deconvolution analysis were greater than those estimated by method III in NW women ($P < 0.02$ for both deconvolution techniques). In contrast, the values calculated by these two methods were similar in obese subjects (Table 3).
R230 COMPARATIVE ANALYSIS OF GH SECRETION RATE

The present study investigates how the analytical approach and associated kinetic assumptions influence the estimation of the pituitary GH secretion rate. In corollary, we evaluated the basis for hyposomatotropinemia in UBO versus LBO women. To this end, we applied several well-known analytical techniques to determine GH secretion rates to 24-h serum GH concentration time series in three groups of women. Two mathematically independent categories of deconvolution analysis predicted a reduction in daily GH secretion (per liter of $V_d$) in UBO compared with NW women, whereas two other integrative models did not suggest this distinction. In addition, deconvolution analysis implied that the reduction in plasma GH concentrations in this cohort of obese women was attributable to reduced GH secretion, whereas the other two methods predicted that elevated metabolic clearance in the obese subjects is the major cause of hyposomatotropinemia. Thus clinical and physiological mechanistic interpretations are critically dependent on the nature of the particular analytical tool applied.

Various considerations may explain the differences between deconvolution-derived secretion rates and those based on exogenous GH injections (method II). Waveform-specific deconvolution analysis estimates the endogenous pseudo-steady-state GH half-life (31), whereas injection methods determine exogenous GH clearance in the face of continuous somatostatin infusion. The plasma clearance of GH that has been inferred from its intravenous (5 min) infusion may not fully reflect endogenous physiology for several reasons. First, exogenous GH clearance rates are usually determined at one specific time of day, whereas deconvolution analysis estimates the mean endogenous GH half-life on the basis of plasma concentration peaks occurring throughout 24 h. Indeed, the plasma half-life of (exogenous) GH can vary by several minutes over 24 h (10). This distinction limits the comparability of data. Second, estimation of GH clearance using a single dose of exogenous GH may neglect the contribution to GH clearance that is concentration dependent (8, 22) Inasmuch as plasma GH levels vary physiologically over 24 h, the “average” daily GH clearance rate may not be reflected faithfully in a single exogenous estimate. Third, given the presence of a high-affinity GH binding protein in plasma, the “time-mode” of GH entry into the bloodstream [i.e., bolus vs. 5-min infusion (as used here) vs. continuous infusion] may also control the apparent GH half-life (24, 33). Fourth, the disappearance of exogenous GH during somatostatin infusion may not mirror that of endogenous GH secreted at pseudosteady state without somatostatin overlay. Somatostatin profoundly depletes plasma GH, alters the endocrine milieu (6), and affects hepato-splanchnic blood flow (25). It is conceivable that one or more of the foregoing variables explicates the disparity in GH secretion rates calculated by deconvolution analysis versus those derived from exogenous GH infusion (above). Finally, one should realize that injection of monocomponent rhGH of 22-kDa molecular mass, and employment of assays that are specific for 22-kDa GH are probably not fully suitable to appropriately appraise the kinetics of the endogenous admixture of 20-/22-kDa molecules and their oligomers (1, 2).

Deconvolution analysis of plasma hormone concentration time series has been validated in various ways as a reliable tool to establish hormone secretion rates (3, 13). However, these techniques also have intrinsic limitations, e.g., they may be half-life or model dependent and do not determine hormone distribution volume. Therefore, deconvolution-derived hormone secretion rates are expressed per unit distribution volume. Unless additional experiments are performed, this normalization can be a disadvantage whenever hormone clearance and the hormone distribution volume covary significantly. For example, we found that the plasma GH clearance rate and distribution volume are simultaneously increased in obese women compared with NW controls, which yields a similar plasma GH half-life in these subjects (16). In this case, deconvolution analysis of plasma GH concentrations expressed per unknown unit distribution volume will underestimate the quantity of hormone released from its source. Accordingly, when absolute secretory quantitation is desired and/or metabolic clearance and $V_d$ covary, the $V_d$ should be determined experimentally to supplement deconvolution estimates. Another consideration in deconvolution-based estimates is the secretory model form chosen. For example, whereas an approximately Gaussian (symmetric) secretory waveform has been validated independently for certain hormones such as cortisol (13), luteinizing hormone (32), and GH (3), in healthy subjects, various disease states, a different hormone type, and the particular sampling location within the circulatory tree, etc. might alter the apparent secretory waveform (12) and/or change the evident admixture of basal and pulsatile hormone secretion (29). Finally, application of a nominal (population mean) GH half-life in waveform-independent deconvolution analysis may not be appropriate when different pathophysiologicals are compared. It is particularly relevant to the present study that the half-life of (exogenous) GH may be reduced and its clearance increased in obese compared with NW humans (16, 30).

Calculation of GH secretion rates based on published body weight-dependent estimates of GH distribution volume, a nominal GH half-life, and 24-h plasma GH concentrations (method III) (9, 19, 20) has a number of limitations. First, the present data show that GH distribution volume is not necessarily correlated with body weight (Fig. 1). Indeed, GH $V_d$ is considerably underestimated when assumed to represent 7% of body weight, so that GH clearance and the extrapolated GH secretion rate are underestimated as well. So far as we are aware, the assumption that the GH distribution space is 7% of body weight is based on the results of limited studies. For example, in one of these studies, only three patients were included (2 with panhypopituitarism and 1 with acromegaly) (20). In another, the majority of subjects who were studied had liver, renal,
or thyroid disease (18). Another deterrent is that GH clearance is assumed to be constant over 24 h, whereas diurnal variability exists (10). Finally, application of a nominal GH half-life in NW and obese subjects may not reflect normal physiology (above).

What then is the appropriate way to determine the endogenous GH secretion rate in humans? The answer to this question depends on the exact aim of the experiment. Deconvolution analysis without further data cannot determine the GH distribution volume and the absolute quantity of GH secreted per unit time. Therefore, if distribution volumes may vary among the study groups and/or quantification of the absolute amount of hormone secreted per unit time is the main goal of an experiment, it is probably best to determine GH distribution volume directly (e.g., by exogenous GH injection) and combine such information with deconvolution analysis or clearance methods (method II). However, the intrinsic limitations of the clearance-estimation technique should be kept in mind. For example, ideally, neurohormone kinetics should be determined endogenously or, if exogenously, using identical mono- or oligomeric hormone whenever possible, a near physiological infusion paradigm (e.g., a continuous infusion of GH with a superimposed 4- to 10-min infusion pulse), hormone infusion dose(s) that achieve the experimentally expected pathophysiological blood levels (e.g., appropriately high in studies of hormone excess and sufficiently low in healthy individuals), an appropriate compartmental kinetic model, and relevant measurement techniques that validly report (and relate) exogenous and endogenous hormone concentrations.

This study demonstrates that estimates of 24-h GH secretion rates in cohorts of healthy NW and UBO and LBO women are not identical among methods. Quite dissimilar inferences can be drawn when different available techniques are applied to the same data sets. Thus we urge caution in the interpretation of hormone secretion rates in humans, especially when estimated under experimental conditions in which significant disparities in hormone kinetic constants (e.g., distribution volume or metabolic clearance) may be encountered among study groups.

Perspectives

Establishment of the secretion rate of hormones is of major importance for proper appreciation of the cause of abnormal concentrations of these hormones in plasma. Inasmuch as alterations of pituitary hormone concentrations play a role in the pathogenesis of a variety of diseases, it is of obvious importance to have appropriate techniques to estimate pituitary hormone secretion rate at one’s disposal. The results of this study underscore the need to reflect on the approach chosen to measure GH secretion, because the kinetic assumptions and limitations intrinsic to each available tool potentially affect the study outcome. The appropriate way to measure GH secretion rate depends on a priori knowledge of GH kinetics in the study populations of interest, the exact intent of the experiment, and the acceptability of various assumptions in that context. In addition, our data urge strong caution in the comparison of GH secretion rates obtained by different methods.

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