A MATHEMATICAL MODEL FOR LOW DOSE OF GHRELIN STIMULATES SYNERGISTICALLY GH-RELEASING HORMONE IN HUMANS BY USING BIVARIATE LOGNORMAL DISTRIBUTION.

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ABSTRACT

Univariate and bivariate lognormal distributions have demonstrated great utility in a number of applications related to decision sciences. In this paper, we utilized a "standardized" form of the univariate and bivariate lognormal distributions for our application part. It is noted that this methodology may be readily extended to the multivariate lognormal distribution also. The synergistic relation between GH-releasing secretagogue (GHS) and GH-releasing hormone (GHRH) with respect to GH secretion is well known. We report a similar relation between GHRH and ghrelin, a recently identified endogenous ligand for the GH receptor. In normal male adults, various doses of ghrelin were intravenously administered alone or together with 1.0 µg/kg GHRH. At small doses of 0.08 and 0.2 µg/kg ghrelin, combined administration of the peptides significantly stimulated GH release in a synergistic manner, the mean GH response values of the two peptide combinations were more than the summed mean GH response values of each peptide alone (P<0.05). By using these results we have arrived conclusion from the mathematical figures given in section 5 for the application part. In medical conclusion they have given that ghrelin synergistically acted with GHRH in humans. This is clearly showed in the mathematical result that the function of GH is monotonically continuous and decreases in the cases of 0.08µg/kg,0.2µg/kg. and 1.0 µg/kg, when time increases.

Keywords: Bivariate lognormal distribution, GH, GHRH, Ghrelin.

Mathematical subject classification: $60G_{xx}$, $62H_{xx}$, $62P_{xx}$.

1. Introduction:

A log -normally distributed random variable is a random variable whose logarithm is normally distributed. Johnson, et.al.,(1994) [9].note that some practitioners maintain "that the lognormal distribution is as fundamental as the normal distribution" and that the lognormal distribution has found applications in fields including the Physical sciences, Life sciences, Social sciences and Engineering. Aitchison and Brown (1957) [1] is the classic reference on the lognormal distribution.Thomopoulos and Johnsons (2003)[9] present a full set of reference tables on the standard lognormal distribution and illustrate their use. Thomopoulos and Longinow (1984) [11] utilize the bivariate lognormal distribution in a structural reliability application. It is the objective of this paper to provide practitioners with more comprehensive tables of the cumulative distribution function of the univariate and bivariate lognormal distributions. Additionally, we illustrate a methodology by which "critical values" of "standardized" lognormal distributions may be determined.

2. Characteristics of lognormal distributions

2.1. Univariate Lognormal Distribution.

Consider a log- normally distributed variables x with mean μ_x and standard deviation σ_x denoted $LN(\mu_x, {\sigma_x}^2)$.the variable y, where

$$y = \ln(x) \tag{1}$$

is normally-distributed with mean μ_y and standard deviation σ_y and is denoted$N(\mu_y, {\sigma_y}^2)$.The probability density function $f(x)$ of the lognormal distribution is given by

$$f(x) = \frac{1}{x\sigma_y\sqrt{2\pi}} e^{-\frac{1}{2}\left[\frac{lnx-\mu_y}{\sigma_y}\right]^2} \tag{2}$$

We know that, when μ_y and σ_y are the corresponding mean and variance for x, then

$$\mu_x = e^{\mu_y + \frac{1}{2}{\sigma_y}^2} \tag{3}$$

$$\sigma_x{}^2 = e^{2\mu_y+\sigma_y{}^2}(\, e^{\sigma_y{}^2} - 1) \quad (4)$$

Similarly, using Equation (1), when μ_x and $\sigma_x$are known for x, the corresponding mean and variance for y can be determined by

$$\mu_y = ln\left(\frac{\mu_x{}^2}{\sqrt{\mu_x{}^2+\sigma_x{}^2}}\right) \quad (5)$$

$$\sigma_y{}^2 \; = \ln\left(1+\frac{\sigma_x{}^2}{\mu_x{}^2}\right) \quad (6)$$

Johnsons, et.al.,(1994)note various ways in which the lognormal distribution has been standardized. In this paper, we study the properties of the "standardized lognormal distribution" that arises when the mean of its normal counterpart is zero.i.e.$\mu_y = 0$ So that y is $N(0, \sigma_y{}^2)$for this case, the mean and variance of x become

$$\mu_x = e^{\frac{1}{2}\sigma_y{}^2} \quad (7)$$

$$\sigma_x{}^2 = e^{\sigma_y{}^2}(\, e^{\sigma_y{}^2} - 1) \quad (8)$$

In the event that the mean of y is not equal to zero, the random variable can be transformed in to standardize from y as follows.$y' = y - \mu_y$ (9)

2.2. Bivariate Lognormal distribution

Considered the variables x_1 and x_2 and $y_1 = \ln(x_1)$ and $y_2 = \ln(x_2)$ with x_1 and x_2 bivariate normal.The mean and standard deviation of y_1 and y_2 are μ_{y_1},$\sigma_{y_1}\mu_{y_2}$and ,σ_{y_2}, respectively.The correlation coefficient between y_1 and y_2 is ρ_y.The pair x_1 and x_2 are distributed as bivariate lognormal and have the distribution$LN(\mu_{y_1}, \mu_{y_2}, \sigma_{y_1}, \sigma_{y_2})$.

When $\mu y_1 = 0$ and $\mu y_2 = 0$, x_1 and x_2 are"standardized" lognormal variables, and the distribution is $LN(0,0, \sigma y_1, \sigma y_2)$.we use this standardized lognormal distribution.

Law and Kelton (2000) show the covariance and correlation of the bivariate lognormal variables

$x_1$andx_2 as follows:

$$\sigma_{x_1,x_2} = e^{\sigma_{y_1}\sigma_{y_2}-1}e^{\mu_{y_1}+\mu_{y_2}+\frac{\sigma_{y_1}{}^2+\sigma_{y_2}{}^2}{2}} \tag{10}$$

$$\rho_x = \frac{e^{\sigma_{y_1}\sigma_{y_2}-1}}{\sqrt{e^{\sigma^2 y_1-1}e^{\sigma^2 y_2-1}}} \tag{11}$$

They further show that the covariance for the related pair of variables y_1 and y_2 from bivariate normal distribution is given by

$$\sigma_{y_1,y_2} = ln\left(1+\frac{\sigma_{x_1,x_2}}{|\mu_{x_1},\mu_{x_2}|}\right) \tag{12}$$

3. Applications

Although GH secretion has been assumed to be mainly regulated by GHRH and somatostain,multiple neurotransmitter pathways as well as a variety of peripheral feedback signals also regulate the secretion by acting directly on the anterior pituitary gland and / or by modulating GHRH or somatostatinrelease, or both from the hypothalamus[5,7].Evidence thatsynergistic GH secretagogues(GHSs) exhibit strong GH-releasing activity by acting both on the pituitary and hypothalamus, where GHS receptors are present suggested the existence of another major, unknown factor involved in the control of somatotroph function[3,6,15].In fact, an endogenous ligand for GHS receptor,gherlin,was discovered and specially stimulated GH secretion both in vitro and in vivo[10].It has recently been shown that ghrelin strongly stimulates GH release in humans[13,16].Ghrelin exhibited a similar time course for GH release to those of GHSs[7,10].The potency of ghrelin for GH release was, in agreement with those of GHSs,much stronger than GHRH[6].When taking into consideration the small molecular weight of ghrelin, it may have more potency per mol for GH release than GHRP-2,one of the most potent GHSs[2,16].This utilizes a well-known synergistic effect of GHSs and GHRH on GH secretion[3,6].It is very reasonable to assume that ghrelin also interacts with GHRH synergistically similar to GHSs.Utilization of the synergistic interaction may have the advantage of minimizing the side effects of ghrelin at the in vivo administration.

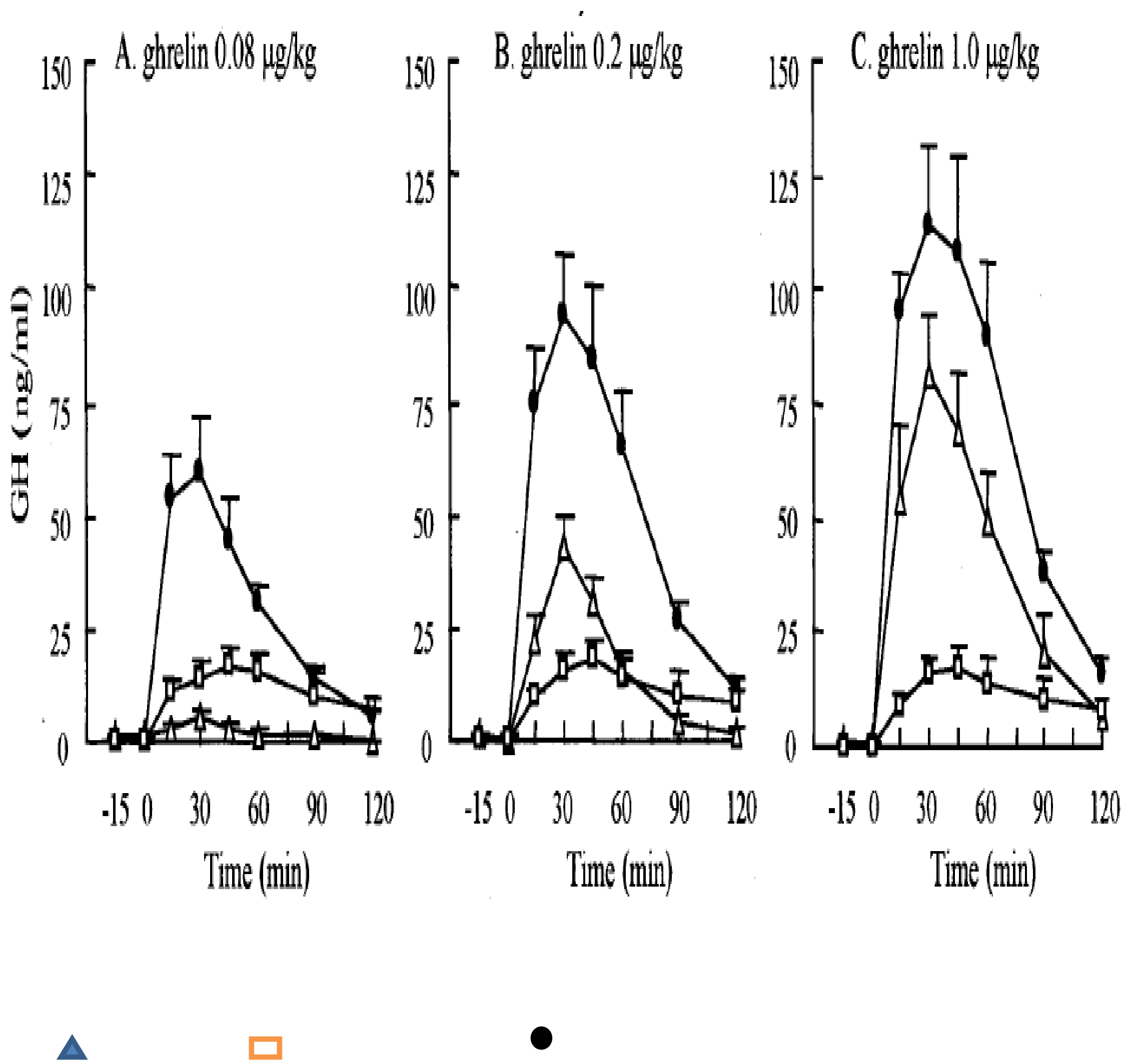


FIG.1.GH levels after ghrelin, GHRH and ghrelin plus GHRH administration (Mean±SEM,n=4).Various doses of ghrelin (A,0.08;B,0.2;C,1.0 µg/kg) were administered alone or in combination with a fixed dose of GHRH,1.0 µg/kg. ghrelin alone; 1.0 µg/kg GHRH; combined administration of ghrelin and 1.0 µg/kg GHRH.

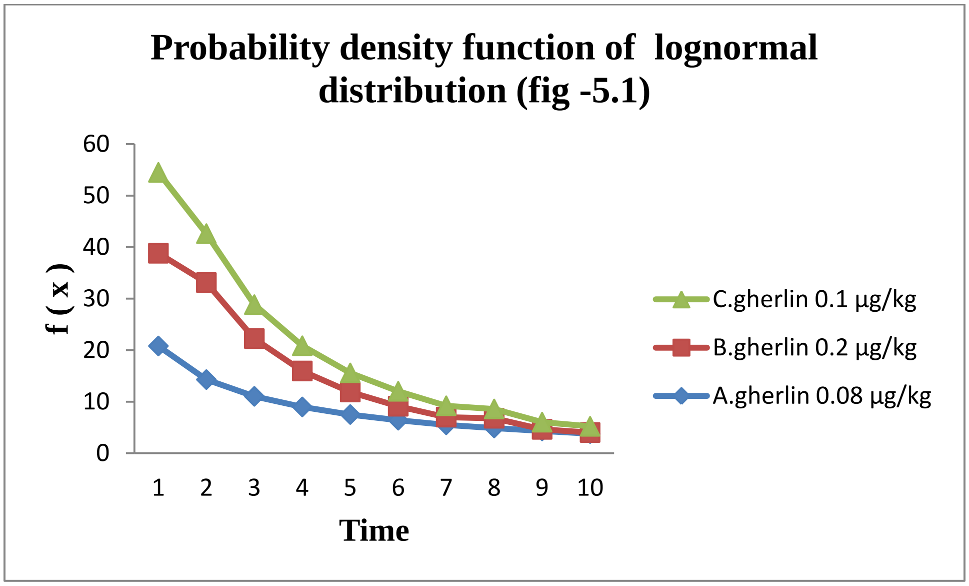
3.1. GH (Growth hormone): Responses to various doses of ghrelin, a fixed dose of GHRH and combinations of the peptides are shown in Fig.1.Ghrelin increased GH release in a dose –dependent manner as described. Previously [7,9].A small stimulation of GH release was elicited by the lowest dose (0.08 µg/kg),but not by 0.04 µg/kg.Although GHRH was administered at the maximally effective dose of 1.0 µg/kg[16,18],ghrelin at doses higher than 0.2 µg/kg tended to increase GH release more than 1.0 µg/kg GHRH(Fig.1)and the different was actually significant at 1 µg/kg ghrelin($P<0.01$).GH responses to combined administration of ghrelin plus GHRH were dose-dependent and ,at any dose of ghrelin greater than those to single administration of ghrelin (Fig.1).Moreover, combined administration of the two peptides stimulated GH release in a synergistic manner.

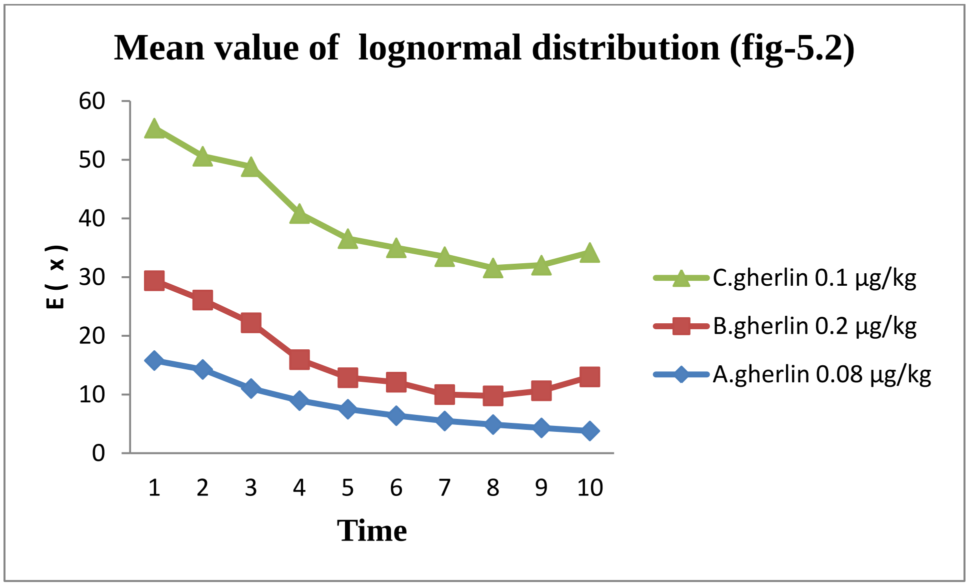
4. Discussion

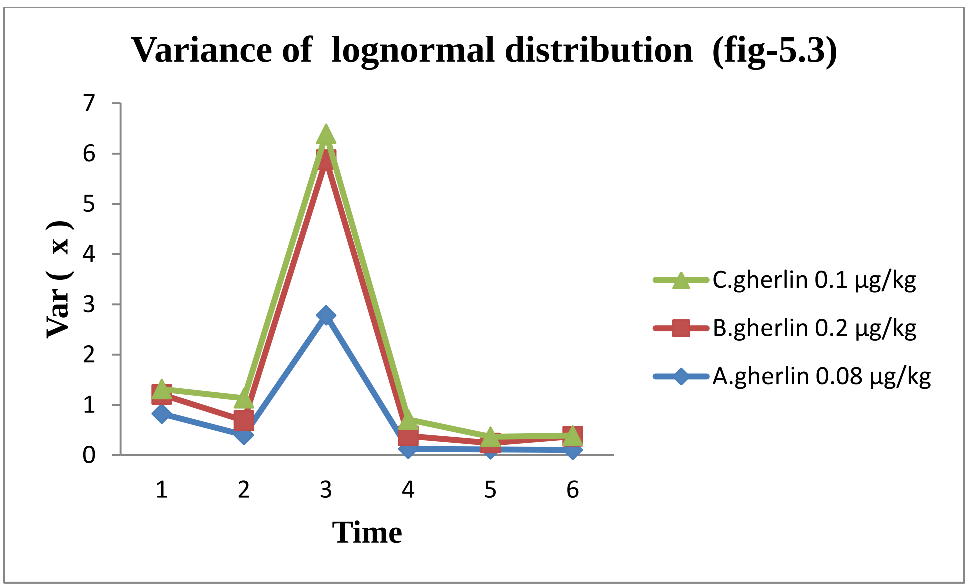
- Here, we clearly demonstrate that ghrelin and GHRH synergistically increased GH release. The synergistic action was most evident at a low dose of ghrelin (0.08 µg/kg or 0.2µg/kg) and 1.0µg/kgGHRH.Findings of a study that tested the co-administration of only a high dose ghrelin(1.0µg/kg)plus 1.0µg/kg GHRH-29 and found a significantsynergistic effect on GH secretion[19].
- According to their findings, however, the difference between the combined administration of the peptides and the sum of the responses to ghrelin and GHRHalone was not marked; GH peak and AUC increased only by 1.05 fold (133.6vs 127.0) and1.26 fold (3,373 vs2, 686), respectively.
- In contrast, we found that a lower dose of ghrelin plus GHRH elicited much greater difference; at 0.2 µg/kg of gherlin.GH peak and AUC increased by 1.51 fold (93.48 vs 62.0) and 1.89 fold (6188 vs 3278),respectively (Fig-1)
- This was also true of co administration of 0.08 µg/kg ghrelin plus GHRH.To avoid the submaximal dose ceiling effect of ghrelin, administration of a low dose ghrelin will be of greater advantage to observe the interaction with GHRH.
- The absolute requirement of a functional GHRH system for GHSs to function as GHS was shown in patients with GHRH receptor deficiency that showed a selective lack of GH response to hexarelin, a potent GHS [22].But requires an operational hypothalamus, suggest that exogenous GHS may induce the release of another hypothalamic factor with GH-releasing capabilities.
- Thus, the synergistic action of ghrelin with GHRH appeared to be specific for GH release, although the activity of ghrelin itself is not fully specific.

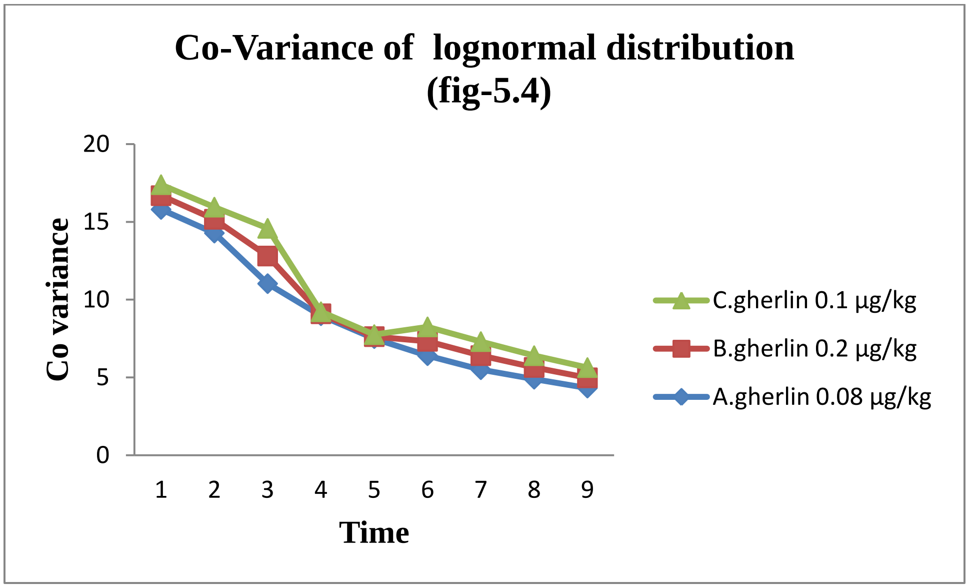
- Considering that ghrelin is an endogenous ligand of GHS-R and a very potent stimulator of GH release, it will be highly reasonable to propose that this hormone, instead of unnatural GHS, should be used for the combined administration.
- In the ghrelin/GHRH test, at most 1.0μg/kg ghrelin combine with 1.0μg/kg GHRH would be adequate to obtain a potent stimulus of GH release. Finally we clearly showed that ghrelin synergistically acted with GHRH in humans.

5. Mathematical Results




Mean value of lognormal distribution (fig-5.2)
60
50
40
30
20
10
0
E (x)
1
2
3
4
5
6
7
8
9
10
Time
C.gherlin 0.1 µg/kg
B.gherlin 0.2 µg/kg
A.gherlin 0.08 µg/kg


Variance of lognormal distribution (fig-5.3)
7
6
5
4
3
2
1
0
Var (x)
1
2
3
4
5
6
Time
C.gherlin 0.1 µg/kg
B.gherlin 0.2 µg/kg
A.gherlin 0.08 µg/kg



6. Conclusion:

This paper gives various measures on the univariate and bivariate lognormal distributions. We show how the lognormal variable is related to a normal variable and its associated standard normal variable. In the same way, the standard bivariate lognormal variables are related to a pair of bivariate normal variables and a pair of standard bivariate variables. We also note how this methodology may be extended to the multivariate lognormal distribution. By using these results we have arrived conclusion from the mathematical figures (5.1, 5.2, 5.3, and 5.4)for the application part. In medical conclusion they have given that ghrelin synergistically acted with GHRH in humans. This coincides with the mathematical result that the function of GH is monotonically continuous and decreases in the case of 0.08µg/kg,0.2µg/kg, 1.0 µg/kg, when time increases.

References

[1].Aitchison, J., and J.A.C.Brown (1957), The Lognormal distribution, Cambridge University Press, Cambridge.

[2].Arvat E, di vitoL,MaccagnoB,et al.(1997). Effects of GHRP-2 and hexarelin,two synthetic GH-releasing peptides, on GH,prolactin,ACTHandcortisol levels in man,Comparison effects of GHRH,TRH and hCRH peptifes.18:885-891.

[3].Bowers CY,VeeraghavanK,Senthumadhavan K.(1993).A typical growth hormone releasing peptides.Newyork:springer-verlag;203-222.

[4].Crow,E.L., and K.Shimizu(1988),Lognormal distributions:Theory and Applications,Marcel Dekker,Newyork.

[5].Giustina.A,Veldhuis JD.(1988). Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human Endocr Rev 19;717-797.

[6].GhigoE,Arvat E ,MuccioliG,Camanni F.(1997). Growth hormone –releasing peptides.Eur J Endocrinol.136:445-460.

[7].GhigoE,ArvatE,GianottiL,MaccarioM,Camanni F(1999). The regulation of growth hormonesecretion.In:JenkinsRC,RossRJM.eds.The endocrine response to acute illness.FrontHorm Res.Basel:karger;24:152-175.

[8].Hines,w.w.,andD.c.Montogomery (1990),Probability and statistics in Engineering and Management science,3rd Edition, John Wiley &sons,Newyork.

[9].Johnson,N.L.,N.Balakrishnan,andS.Kotz(1994),continuous Univariate distributions 1, 2nd Edition, John Wiley &sons,Newyork.

[10].Kojima M,HosadaH,DataY,NakazatoM,MatsuoH,kankawa K.(1999).Gherlin is a growth hormone releasingacylated peptide from stomatch.Nature.402:656-660.

[11].Law,A.M.,andW.D.Kelton (2000),Simulation Modeling and analysis,3rd Edition,M.C.GrawHill,Bosten.

[12].Mahajan T,Lightman SL.(2000).A simple Test for growth hormone deficiency in Adults.J.EndocrinolMetab 85:1473-1476.

[13].PeinoR,BaldelliR,Rodriguez-Garcia J,et al.(2000). Gherlin-induced growth hormone secretion in humans.Eur J Endocrinol.143:R11-14.

[14].PopovicV,LealA,MicicD,et.al(2000) GH-releasing hormone and GH releasing peptide-6 for diagnostic testing in GH deficient adults.Lancet.356:1137-1142.

[15].Smith RG,Van der PloegLXT,HowardAD,et.al(1997). Peptidomimetic regulation of growth hormone secretion.Endicrionol.Rev.18:621-645.

[16].Takaya K,AriyasuH,KanamotoN,et.al(2000). Gherlin strongly stimulates growth hormone release in humans ClinEndocrinolMetab 85:4908-4911.