International Journal of Applied and Advanced Scientific Research (IJAASR)
Impact Factor: 5.255, ISSN (Online): 2456 - 3080
(www.dvpublication.com) Volume I, Issue I, 2016

A NEW STOCHASTIC MODEL TO ESTIMATE THE INFLUENCE OF INSULIN ON CIRCULATING GHRELIN USING GAMMA DISTRIBUTION

Dr. P. Senthil Kumar*, K. Balasubramanian & A. Dinesh Kumar*****

* Assistant Professor of Mathematics, Rajah Serfoji Government College (Autonomous), Thanjavur, Tamilnadu

** Assistant Professor of Mathematics, Anjalai Ammal Mahalingam Engineering College, Kovilvenni, Thiruvarur, Tamilnadu

*** Assistant Professor of Mathematics, Dhanalakshmi Srinivasan Engineering College, Perambalur, Tamilnadu

Cite This Article: Dr. P. Senthil Kumar, K. Balasubramanian & A. Dinesh Kumar, "A New Stochastic Model to Estimate the Influence of Insulin on Circulating Ghrelin Using Gamma Distribution", International Journal of Applied and Advanced Scientific Research, Page Number 4-8, Volume 1, Issue 1, 2016

Abstract:

Ghrelin is a novel peptide that acts on the growth hormone (GH) secretagogue receptor in the pituitary and hypothalamus. It may functions as a third physiological regulator of GH secretion, along with GH-releasing hormone and somatostatin. In addition to the action of ghrelin on the GH axis, it appears to have a role in the determination of energy homeostasis. Although feeding suppresses ghrelin production and fasting stimulates ghrelin release, the underlying mechanisms controlling this process remain unclear. Our data suggest that insulin may suppress circulating ghrelin independently of glucose, although glucose may have an additional effect. The purpose of this study was to estimate the influence of insulin on circulating ghrelin using gamma distribution with the help of duality principle.

Key Words: Insulin, Ghrelin, Duality Principle & Gamma Distribution

1. Introduction:

Ghrelin is a novel peptide that acts on the growth hormone (GH) secretagogue receptor in the pituitary and hypothalamus, possibly functioning as a third physiological regulator of GH secretion along with GH releasing hormone (GHRH) and somatostatin. In addition to the action of ghrelin on the GH axis, it appears to have a role in the determination of energy homeostasis [1-2] & [4]. Ghrelin acts as an orexigenic hormone, stimulating both neuropeptide Y (NPY) and agoutirelated peptide, and thus feeding [6-7]. Although feeding suppresses ghrelin production and fasting stimulates ghrelin release, the underlying mechanisms controlling these processes remain unclear [9-10]. This relationship is the opposite of that seen with leptin [11], which has been shown to be increased by insulin [11]. Specifically, the roles that alterations in plasma glucose and insulin have in regulating ghrelin secretion have not been established. The purpose of this study was to estimate the influence of insulin on circulating ghrelin using gamma distribution with the help of duality principle. This paper classifies a doubly controlled process of servicing machines. The classical system treated by Talkacs is equipped with $m+1$ unreliable machines served by one repairman. In the present modification of this model, the failure rates and the repair time may be controlled with respect to the state of the system. The process describing the number of intact machines is considered. To derive its steady state distribution in the form of a simple explicit formula, the author introduces an auxiliary model with m unreliable machines and a single repairman who keeps working even when all machines are intact. This result is based on a duality principle applied to the process above.

2. Stochastic Model:

In [5] the author studied a multi-channel loss queueing system with control of input stream and service. The servicing facility of the system contained m parallel channels processing a stream of singly arriving customers. No customer was accepted when the servicing facility was occupied. The input stream and service were subject to a comprehensive control. This model can also be interpreted as a system of m unreliable machines served by a single repairman with corresponding service and failure rates control. More specifically, each of the working machines can break down with a rate dependent on the total number of intact machines. The repair time also depends upon the number of intact machines. The repairman is not idle even when all machines become intact. At these times the repairman leaves the system and comes back later with a new machine that immediately replaces an available defective machine. If no machine breaks down during the repairman's absence, a substitution takes place at the repairman's own choice, but the number of working machines does not change and this action is supposed not to affect the future status of the system. Since the repairman leaves the system to get new equipment, we can restrict his absence to a definite time. So the control can particularly be applied to this situation. Besides the clear advantages of this system as a doubly controlled transportation servicing model, it can also be viewed as a doubly controlled model of servicing machines.

Another more popular model of servicing machines with idle periods is one with $m + 1$ machines and with a single repairman who is either repairing defective machines or simply keeping watch when all $m + 1$ are intact. However, he is alert to start his service as soon as any working machine fats. Such a system is probably more practical than the one described above although obviously with a more difficult analysis. Without control it was originally set and studied by [8].

3. Model Description:

Model 1: The system consists of $m + 1$ unreliable machines served by a single repairman. Denote by Z_t^1 the number of intact machines at time $t \geq 0$. When the repair of a last defective machine is completed and the total number of intact machines becomes $m + 1$, the repairman is idle until the next breakdown. Let $\tau_1, \tau_2, \ldots$ be the successive instants of the completion of machine repairs. The repair time of the nth machine is distributed in accordance with $A\, \xi_n(x) \in \{A_k(x); k = 0,1, \ldots, m\}$ (a tuple of arbitrary $d.f.$'s), where $\xi_n := Z_{\tau_n}^1, n = 1,2, \ldots$. That is, the repair time depends upon the number of intact machines at the moment immediately before the completion of the preceding service. The working machines perform certain jobs. Within the interval $[\tau_n, \tau_{n+1})$ the continuous durations of each job are conditionally independent given ξ_n and exponentially distributed with parameter $\mu_{\xi_n} \in \{\mu_k, k = 0,1, \ldots, m + w\} \subset \mathbb{R}_+ \setminus \{0\}$.

Model 2: There are a maximum of m working unreliable machines and one repairman. The total number of intact machines at time $t \geq 0$ is denoted by Z_t. Unlike Model 1, there are no idle periods. At certain epochs of time the repairman temporarily abandons the system to acquire a new machine. Let T_n be an epoch when a machine is completely repaired. If at this time the total number of intact machines is m, the repairman leaves the system and returns to the system at time $T_{n+1}$with a new machine to replace any machine that has failed during the repairman's absence. In other words, if the repairman returns to fewer than m working machines, then the number of working machines increases by one. If no machine has failed to this time, a replacement still occurs but at the repairman's own choice (in this case, without any effect on the system). In both cases used machines arc removed from the system. Consequently, $T_1, T_2, \ldots$ are the moments when the repairman completes a job (repair of a machine or acquisition of new equipment). At time T_n he begins with the repair of a current machine or leaves the system if no defective machine is available. At the time T_{n+1} he completes the repair or returns to the system with a new machine. The length of the interval $[T_n, T_{n+1})$ is distributed according to the $d.f.$

$$A_{X_n}(x) \in \{A_k(x); k = 0,1, \ldots, m\} \qquad (1)$$

where

$$X_n := Z_{T_n}, n = 0,1, \ldots \qquad (2)$$

For instance, control can be applied to the period of the repairman's absence distribute differently from the repair time. The assumption about the failure rates is as in Model 1. Namely within the interval $[T_n, T_{n+1})$ the continuous durations of each job are conditionally independent given X_n and exponentially distributed with parameter

$$\mu_{x_n} \in \{\mu_k, k = 0,1, \ldots, m + w\} \subset \mathbb{R}_+ \setminus \{0\} \qquad (3)$$

As mentioned, this model is identical to the doubly controlled m −channel loss queueing system studied by the author [5], where Z_t denotes the number of customers in the system at time t. To explain equivalence between both systems, we use the mutual notation below. At time T_n a customer departs from a source and at time T_{n+1} arrives at the system. The customer is served by one of the free parallel channels available, or is lost by the system if the servicing facility is busy. The length of the interval $[T_n, T_{n+1})$ is distributed as in (1) and (2), and the servicing policy is determined by (3). Within the interval $[T_n, T_{n+1})$ the service durations of customers in each of the channels are conditionally independent given X_n and exponentially distributed with parameter μ_{X_n}.

4. Connection between the Models:

It can be shown that $\tau_1, \tau_2, \ldots$ is a sequence of stopping times relative to the canonic filtering $\sigma(Z_u^1; u \leq t)$, that $T_1, T_2, \ldots$ is a sequence of stopping times relative to $\sigma(Z_u; u \leq t)$, and that the processes $\left(\Omega_1, \mathfrak{U}_1, (P^x)_{x \in E_1}, (Z_t^1; t \geq 0)\right) \to E_1 = \{0,1, \ldots, m + 1\}$ and $\left(\Omega, \mathfrak{U}, (P^x)_{x \in E}, (Z_t; t \geq 0)\right) \to E = \{0,1, \ldots, m\}$ are semi-regenerative relative to these sequences ($cf.$ definition in [5]). Consequently, $\left(\Omega_1, \mathfrak{U}_1, (P^x)_{x \in E}, (\xi_n; \mathrm{n} = 1,2, \ldots)\right) \to E$ and $\left(\Omega, \mathfrak{U}, (P^x)_{x \in E}, (X_n; \mathrm{n} = 1,2, \ldots)\right) \to E$ are embedded Markov chains (MC). Since the idleness of the repairman in the first model is distributed exponentially, it is easy to see that both MC's are stochastically equivalent and they are obviously ergodic. Let $\left(\Omega_1, \mathfrak{U}_1, (P^x)_{x \in E}, (Y_t^1; \mathrm{t} \geq 0)\right) \to E_1$ and $\left(\Omega, \mathfrak{U}, (P^x)_{x \in E}, (Y_t; t \geq 0)\right) \to E$ be the semi-Markov processes associated with the sequences of stopping times above. Both are ergodic and their limiting probabilities are expressed through the invariant probability measure P of the MC(X_n) or the MC(ξ_n). (Since (X_n) and (ξ_n) are stochastically equivalent, only one of them, say (X_n), will be mentioned further.) Next we need the limiting probabilities

$$y_k^1 := \lim_{t \to \infty} P^x\{Y_t^1 = k\} = \frac{P_k M_k}{PM}, k \in E \qquad (4)$$

($cf.$ Cinlar [3]) where M_k can be easily derived as

$$M_k := E^k[T_1] = \begin{cases} a_k & , k = 0,1, \ldots, m - 1 \\ a + \frac{1}{\mu(m+1)}, & k = m \end{cases} \qquad (5)$$

and PM is the scalar product of P and $M = (M_0, M_1, \ldots, M_m)^T$ which can be expressed the formula

$$= PA + P_m \frac{1}{\mu(m+1)}. \quad (6)$$

The duality principle between Models 1 and 2 is based on the following consideration. Let $\mathcal{B}_n$ and $\mathcal{I}_n$ denote the nth busy period and the idle period following the nth busy period, respectively, in Model 1. Let $\mathcal{C}_t; t \geq 0$ be the counting process associated with the point process $\{\mathcal{B}_n; n = 1,2,\dots\}$. It is readily seen that the processes Z_t and Z_t^1 during their busy periods are stochastically equivalent or formally $P^x\{Z_t = k\} = P^x\{Z_t^1 = k/\mathcal{I}_{\mathcal{C}_t} > t\}, k \in E$, where the probability $P^x\{Z_t^1 = k/\mathcal{I}_{\mathcal{C}_t} > t\}$ can be expressed as

$$P^x\{Z_t^1 = k/\mathcal{I}_{\mathcal{C}_t} > t\} = \frac{P^x\{Z_t^1 = k,\ Z_t^1 \in \{0,1,\dots,m\}\}}{P^x\{Z_t^1 \in \{0,1,\dots,m\}\}}$$

$$= \begin{cases} 0 & , k = m+1 \\ \frac{P^x\{Z_t^1 = k\}}{1 - P^x\{Z_t^1 = m+w+1\}} & , k \leq m \end{cases}.$$

Therefore,

$$P^x\{Z_t^1 = k\} = [1 - P^x\{Z_t^1 = m+1\}]P^x\{Z_t = k\}, k = 0,1,\dots,m. \quad (7)$$

We now find $P^x\{Z_t^1 = m+1\}$.

$$P^x\{Z_t^1 = m+1\} = P^x\{Y_t^1 = m\}P^x\{\mathcal{I}_{\mathcal{C}_t} \leq t/Y_t^1 = m\} \quad (8)$$

where

$$\lim_{t\to\infty} P^x\{\mathcal{I}_{\mathcal{C}_t} \leq t/Y_t^1 = m\} = \frac{1}{1+a\mu(m+1)}. \quad (9)$$

Let $\pi_k^1 := \lim_{t\to\infty} P^x\{Z_t^1 = k\}$. Then from (4) - (6), (8) and (9) it follows that

$$\pi_{m+1}^1 = \frac{P_m}{PA\mu(m+1) + P_m}. \quad (10)$$

Finally, (7) and (10) yield

$$\pi_k^1 = (1 - \pi_{m+1}^1)\pi_k, k = 0,1,\dots,m \quad (11)$$

where $\pi_k = \lim_{t\to\infty} P^x\{Z_t = k\}$ was obtained in [5].

5. Model Examples:

(i) Recall that in case of Model 2 the repairman leaves the system when all machines are intact. However, the repairman may plan to leave for only a short duration. Assume his expected absence is $= a_m \leq \frac{1}{\mu m}$. Here both a and μ can be adjusted if necessary. For example,

$$\mu_j = \begin{cases} \mu_0, j = 0,1,\dots,m-1 \\ \mu, \quad\quad j = m \end{cases}$$

while $A_j(x)$ is subject to no restriction.

(ii) An undesirable situation occurs if during the repairman's absence the number of working machines falls below the level $m - r, r = 0,1,\dots,m-1$. We calculate the probability of this event as

$$\gamma_r := \lim_{t\to\infty} P^x\{Y_t = m, Z_t < m - r\} = \sum_{n=0}^{m} \pi_{m,n} - \sum_{n=m-r}^{m} \pi_{m,n}. \quad (12)$$

To derive γ_r we observe that the first sum above is

$$y_m^2 := \lim_{t\to\infty} P^x\{Y_t = m\} = \frac{aP_m}{PA} \quad (13)$$

($cf.$ the similar formula (4))

Also from [5] one can derive by the summation of the equations

$$PAn\,\pi_{jn} = \frac{1}{\mu_j}\sum_{k=0}^{n-1} P_j\, p_{jk}\ , 1 \leq n \leq \min\{j+1, m\}, j \in E. \quad (14)$$

Therefore, from (12) - (14) and [5] we have

$$\gamma_r = \frac{P_m}{PA}\left[a - \frac{1}{m\mu}\sum_{n=m-r}^{m}\sum_{k=0}^{n-1} P_{m,k}\right]\mathrm{T},$$

(iii) Now we return to the relation between the models. Formulas (10), (11) and [5] can be combined to obtain the corresponding stationary probabilities π_k^1. An elegant expression follows when $\mu_j = \mu, j \in E$: (15)

$$\pi_k^1 = \frac{(m+1)P_{k-1}}{k[PA\,\mu(m+1) + P_m]}, k = 1,\dots,m+1$$

And finally, when $PA = a(i.e.\, a_j = a)$, (15) implies Takacs' well known formula [8].

$$\pi_k^1 = \frac{(m+1)P_{k-1}}{k[a\mu(m+1) + P_m]}, k = 1,\dots,m+1 \quad (16)$$

where the $d.f.$'s $A_j(x)$ are still arbitrary and possibly distinct and thus (16) holds under more general conditions.

6. Example:

Eleven young adult volunteers (9 women, 2 men) participated in the study. The age of the subjects was 24 ± 4 yr (range 18–31 yr), and the body mass index was 22.1 ± 2.8 kg/m2 (18.4–26.6 kg/m2). All subjects were healthy and taking no medication. They were instructed to maintain their normal physical activity and to consume a normal diet containing

≥200 g of carbohydrate for 3 days before the study. Before the study, a small Teflon catheter was inserted into an antecubital vein for infusion of insulin and glucose. A second catheter was inserted in a retrograde direction into a wrist vein in the opposite arm for blood sampling. This was kept patent with a slow infusion of isotonic saline. The hand was then placed in a heated box to achieve a temperature of 65°C to obtain arterialized blood through the wrist catheter. After a baseline period of 1 h, a three step euhypohyperglycemic glucose clamp was then performed (6). A primed continuous infusion of insulin was administered at a rate of 1 $mU^{-1}kg^{-1}$ min^{-1}. Each step of the study was maintained for 60 min, with a 15-min period of adjustment between steps. Throughout the study, plasma glucose concentrations were monitored every 5 min and used to regulate plasma glucose by the adjustment of a variable infusion of 20% dextrose. Plasma glucose was maintained at 90 mg/dl during the euglycemic phase of the study, at 50 mg/dl during hypoglycemia, and at 160 mg/dl during hyperglycemia. Two samples for measurement of insulin, GH, and ghrelin were taken in the hour preceding the study and repeated during the three steps of the clamp procedure. The glucose and insulin data from these studies are included in another study that examined the accuracy of glucose sensor measurements (7).

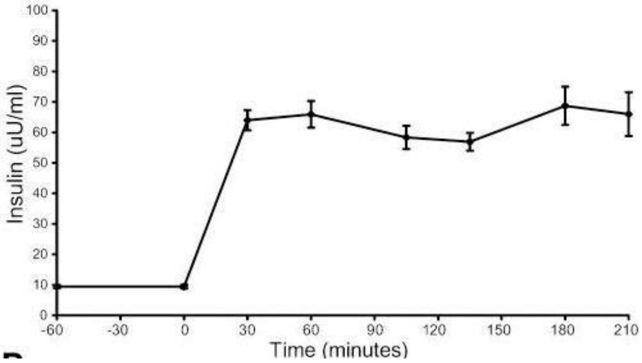

Figure (1): Insulin concentrations during a stepped euhypohyperglycemic glucose clamp.

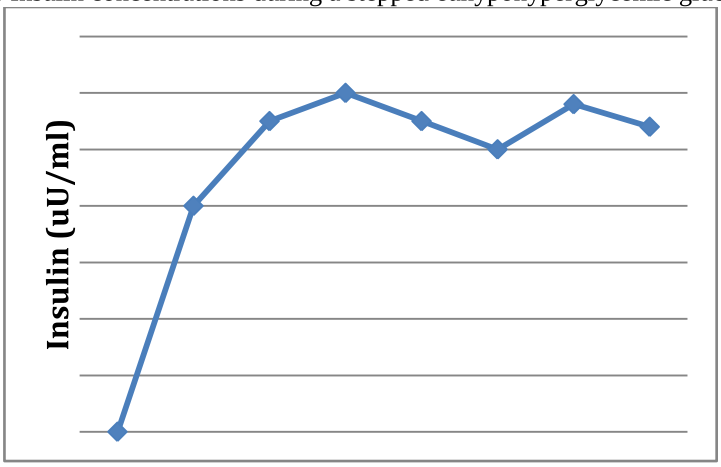

Figure (2): Insulin concentrations during a stepped euhypohyperglycemic glucose clamp (Using Gamma Distribution)

7. Conclusion:

It has been repeatedly demonstrated that circulating GH levels are reduced in obese subjects who are insulin resistant and hyperinsulinemic. We have reported that such compensatory hyperinsulinemia suppresses IGF-binding protein-1 levels, which in turn may lead to increased bioavailability of free IGF-I and feedback suppression of GH secretion. It is intriguing to speculate that insulin-induced suppression of ghrelin may also play a role in the reduction in GH secretion observed in obesity. Duality principle with normal distribution gives the same as the medical report. There is no significance difference between medical and mathematical reports. The medical reports are beautifully fitted with the mathematical model. Hence the mathematical report {Figure (2)} is coincide with the medical report {Figure (1)}.

8. References:

1. Attia N, Tamborlane W V, Heptulla R, Maggs D, Grozman A, Sherwin R S & Caprio S, "The metabolic syndrome and insulin-like growth factor I regulation in adolescent obesity", Journal of Clinical Endocrinology Metabolism, Volume 83, Page Number 1467–1471, 1998.
2. Barbetti F, Crescenti C, Negri M, Leonetti F, Grossi A & Tamburrano G, "Growth hormone does not inhibit its own secretion during prolonged hypoglycemia in man", Journal of Clinical Endocrinology Metabolism, Volume 70, Page Number 1371–1374, 1990.
3. Cinlar E, "Introduction to Stochastic Processes", Prentice Hall, Englewood Cliffs, New York, 1975.

4. DeFronzo R A, Tobin J D & Andres R, “Glucose clamp technique: a method for quantifying insulin secretion and resistance”, American Journal of Physiology Endocrinology Metabolism, Number 237, Page Number 214–223, 1979.
5. Dshalalow J, “On a Multi Channel Transportation Loss System with Controlled Input and Controlled Service”, Journal of Applied Mathematics and Simulation, Volume1, Number 1, Page Number 41-55, 1987.
6. Jaffe C A, DeMott Friberg R & Barkan A L, “Endogenous growth hormone (GH) releasing hormone is required for GH responses to pharmacological stimuli”, Journal of Clinical Investigation, Volume 97, Page Number 934–940, 1996.
7. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H & Kangawa K, “Ghrelin is a growth hormone releasing acylated peptide from stomach”, Nature, Number 402, Page Number 656–660, 1999.
8. Takacs L, “Introduction to the Theory of Queues”, Oxford University Press, 1962.
9. Tannenbaum G S, Martin J B & Colle E, “Ultradian growth hormone rhythm in the rat: effects of feeding, hyperglycemia, and insulin-induced hypoglycemia”, Endocrinology, Number 99, Page Number 720–727, 1976.
10. Thorner M O, Chapman I M, Gaylinn B D, Pezzoli S S & Hartman M L, “Growth hormone releasing hormone and growth hormone releasing peptide as therapeutic agents to enhance growth hormone secretion in disease and aging”, Recent Prognosis Homology, Number 52, Page Number 215–244, 1997.
11. Trayhurn P, Hoggard N, Mercer J G & Rayner D V, “Leptin: fundamental aspects”, International Journal of Obese Related Metabolism Disorders, Volume 23, Supplementary, Number 1, Page Number 22–28, 1999.