

A New Mathematical Model to Estimate the Effects of Lipid Induced Insulin Resistance on UPR mRNA Using Normal Distribution

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Abstract: *In this paper we examined effects of lipid induced insulin resistance on insulin stimulation of endoplasmic reticulum (ER) stress. mRNAs of several ER stress markers were determined in fat biopsies obtained before and after 8-h hyperglycemic hyperinsulinemic clamping in 13 normal subjects and in 6 chronically insulin resistant patients with type 2 diabetes mellitus (T2DM). In normal subjects, hyperglycemia hyperinsulinemia increased after/before mRNA ratios of several ER stress markers. Lipid infusion was associated with inhibition of the PI3K insulin signaling pathway and with a decrease of hyperinsulinemia induced ER stress responses. In chronically insulin resistant patients with T2DM, hyperglycemic hyperinsulinemia did not increase ER stress response marker mRNAs. Single server queue with random accumulation level and analysis of the continuous time parameter process is used to find the effects of lipid induced insulin resistance on UPR mRNA with the help of normal distribution.*

Key Words: *Insulin, Endoplasmic Reticulum, Type 2 Diabetes Mellitus, Single Server Queue & Normal Distribution.*

I. INTRODUCTION

Endoplasmic reticulum (ER) stress is increased in adipose tissue of obese rodents [9], [13] & [14] and humans [3], [8] & [18] and has been associated with several obesity related pathologies including type 2 diabetes mellitus (T2DM), hypertension, atherogenic dyslipidemia, and nonalcoholic fatty liver disease [9], [12], [13] & [14]. The reason why ER stress is increased in obesity is complex and includes hypoxia, inflammation [10], and hyperinsulinemia. We recently showed that short term physiologic increases in circulating insulin up regulated the unfolded protein response (UPR), an adaptive ER stress response that reflects ER stress, in subcutaneous adipose tissue of normal subjects, dose dependently over the entire physiological insulin range. Whether the chronic hyperinsulinemia in insulin resistant subjects has similar effects on ER stress responses is not known and depends on the mechanism through which insulin stimulates ER stress. Hence, if insulin signaling occurred through the so called metabolic, (i.e) the phosphoinositide 3-kinase (PI3K) pathway, one would expect little or no insulin effect on ER stress in obese subjects or in patients with T2DM, in whom this pathway is inhibited. If, on the other hand, insulin signaling occurred via alternate pathways, collectively called mitogen activated protein kinase pathways, insulin could increase ER stress even in “insulin resistant” subjects. Instances of such “selective insulin resistance,” (i.e) resistance in the metabolic/PI3K pathway and normal or increased activity in an alternate insulin signaling pathway, are increasingly being recognized [5] & [11]. To differentiate between these possibilities, we examined effects of hyperinsulinemia on ER stress markers in subcutaneous adipose tissue of normal subjects in whom the metabolic/PI3K pathway was inhibited with lipid infusion and in subcutaneous adipose tissue of insulinresistant patients with T2DM, in whom the metabolic/ PI3K pathway is known to be inhibited. In a large class of bulk queueing models, the server takes groups of a fixed size for service if enough group members are available; otherwise, it waits until the queue reaches a desired level. Several versions of such systems are considered in [6] & [7]. We call such systems queues with fixed accumulation level. Practically more attractive and versatile, but analytically more complicated, is a system with a random accumulation level. In such a system, the server capacity is a random number generated by the completion of previous service and this number is the desired group size to be taken for service. The server will therefore rest until the queue accumulates that many customers if that group size is unavailable by the time the server becomes free.

For instance, for shipment of certain goods not only are transportation units of different capacity used, but arriving units can also be partially occupied. Units can take some of the load and move that quantity farther, or wait until the load reaches a specified level.

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Although such situations are most common in air and surface transportation, postal delivery, inventory transportation systems and assembly lines, there are other real systems of the same nature that can be modeled by queues with random accumulation levels. For example, a computer user needs a specific task to be performed on several parallel or networked computers or processors. The job can only be started when all necessary computer components become free. So in this case the job to be done will be regarded as a server and computers will play the role of the customers. Again each particular job needs a different number of computers. Thus the situation can be described in terms of a model with a random accumulation level. In this paper we find the effects of lipid induced insulin resistance on UPR mRNA by using Single server queue with random accumulation level and analysis of the continuous time parameter process with the help of normal distribution.

II. ASSUMPTIONS AND BASIC DEFINITIONS

A. Definition

Let T be a stopping time for a stochastic process $\{\Omega, \mathcal{F}, (P^x)_{x \in E}, Z(t); t \geq 0 \rightarrow (E, \mathfrak{B}(E))\}$. $\{Z(t)\}$ is said to have the locally strong Markov property at T if for each bounded random variable $\zeta: \Omega \rightarrow E^r$ and for each Baire function $f: E^r \rightarrow \mathbb{R}, r = 1, 2, \dots$, it holds true that $E^x[f \circ \zeta \circ \theta_T / \mathcal{F}_T] = E^{Z_T}[f \circ \zeta] P^x - a. s. \text{ on } \{T < \infty\}$, where θ_y is the shift operator.

B. Definition

A stochastic process $\{\Omega, \mathcal{F}, (P^x)_{x \in E}, Z(t); t \geq 0\} \rightarrow (E, \mathfrak{B}(E))$ with $E \leq N$ is called semi-regenerative if there is a point process $\{t_n\}$ on \mathbb{R}_+ such that $t_n \rightarrow \infty (n \rightarrow \infty)$ and such that each t_n is a stopping time relative to the canonic filtering $(Z_y; y \leq t)$,
 The process $(Z(t))$ has the locally strong Markov property at $t_n, n = 1, 2, \dots$,
 $\{Z(t_n + 0), t_n; n = 0, 1, \dots\}$ is a Markov renewal process.

C. Definition

Let (X_n, t_n) be an irreducible aperiodic Markov renewal process with a discrete state space E . Denote $\beta_x = E^x[t_1]$ as the mean sojourn time of the Markov renewal process in state $\{x\}$ and let $\beta = (\beta_x; x \in E)^T$. Suppose that the imbedded Markov chain (X_n) is ergodic and that P is its stationary distribution. We call $P\beta$ the mean inter renewal time. We call the Markov renewal process recurrent positive if its mean inter renewal time is finite. An irreducible aperiodic and recurrent positive Markov renewal process is called ergodic.

D. Definition

Let $\{\Omega, \mathcal{F}, (P^x)_{x \in E}, Z(t); t \geq 0\} \rightarrow (E, \mathfrak{B}(E))$ be a semi regenerative process relative to the sequence $\{t_n\}$ of stopping times. Introduce the probability $K_{jk}(t) = P^j\{Z(t) = k, t_1 > t\}, j, k \in E$. We will call the functional matrix $K(t) = (K_{jk}(t); j, k \in E)$ the semi regenerative kernel.

E. Theorem

Let $\{\Omega, \mathcal{F}, (P^x)_{x \in E}, Z(t); t \geq 0\} \rightarrow (E, \mathfrak{B}(E))$ be a semi regenerative stochastic process relative to the sequence $\{t_n\}$ of stopping times and let $K(t)$ be the corresponding semi regenerative kernel. Suppose that the associated Markov renewal process is ergodic and that the semi regenerative kernel is Riemann integrable over \mathbb{R}_+ . Then the stationary distribution $\pi = (\pi_x; x \in E)$ of the process $(Z(t))$ exists and it is determined from the formula: $\pi_k = \frac{1}{P\beta} \sum_{j \in E} P_j \int_0^\infty K_{jk}(t) dt, k \in E$ [4].

F. Corollary

Denote $H = (h_{jk}; j, k \in E) = \int_0^\infty K(t) dt$ as the integrated semi regenerative kernel, $h_j(z)$ the generating function of j th row of matrix H and $\pi(z)$ as the generating function of vector π . Then the following formula holds true.

$$\pi(z) = \frac{1}{P\beta} \sum_{j \in E} P_j h_j(z)$$

G. Proof

From (2.5) we get an equivalent formula in matrix form, $\pi = \frac{PH}{P\beta}$. Finally, formula (2.6) is the result of elementary algebraic transformations.

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III. DESCRIPTION OF THE SYSTEM AND NOTATION

Let $Q(t)$ denote the number of customers in a single-server queueing system at time $t \geq 0$ and let $Q_n = Q(t_n + 0), n = 1, 2, \dots$, where t_n is the moment of time when the server completes the processing of the n^{th} group of customers. At time $t_n + 0$ the server can carry a group of customers of size c_{n+1} and it takes that many for service if available. If not available, that is if $Q_n < c_{n+1}$, the server prefers to rest as long as necessary for the queue to accumulate to the level of c_{n+1} . Only then does it begin to process a group of the appropriate size, with the pure service time lasting $\sigma_n + 1$. We assume that each of the sequences $\{c_n\}$ and $\{\sigma_n\}$ are families of independent identically distributed random variables, independent of each other and of the input stream. The probability distribution of c_1 is given by $g_k = P\{c_1 = k\}, k = 1, 2, \dots, r$. The random variable σ_1 has an arbitrary probability distribution function B , with $B(x) = 0$ for $x < 0$, and with a finite mean b . We denote

$$g(x) = E[x^{c_1}]$$

$$\beta(\theta) = \int_0^\infty e^{-\theta x} B(dx), \Re(\theta) \geq 0$$

The input stream is formed by an orderly stationary Poisson point process $\{r_n\}$ with intensity λ ; and the capacity of the waiting room is assumed to be unlimited.

IV. IMBEDDED PROCESS

Let $N(\cdot)$ denote the counting measure associated with the point process $\{r_n\}$. Denote $v_n = N(\sigma_n)$. Then the terms of the sequence $\{Q_n\}$ satisfy the following recursive relation:

$$Q_{n+1} = \begin{cases} Q_n + (c_{n+1} - Q_n) + v_{n+1} - c_{n+1}, & Q_n < c_{n+1} \\ Q_n - c_{n+1} + v_{n+1}, & Q_n \geq c_{n+1} \end{cases} \quad (1)$$

Clearly the process $\{\Omega, \mathcal{F}, (P^x)_{x \in E}, Q(t); t \geq 0\} \rightarrow E = \{0, 1, \dots\}$ possesses a locally strong Markov property at t_n (See Definition 2.1), where t_n is a stopping time relative to the canonic filtering $(Q(y); y \leq t), n = 1, 2, \dots$. Thus the imbedded process $\{Q_n\}$ is a homogeneous Markov chain with the transition probability matrix $A = (p_{ij}; i, j \in E)$. Due to (1) the upper block $(p_{ij}; i = 0, 1, \dots, r-1, j \in E)$ of A consists of purely positive elements, and the lower block of A is an upper triangular matrix. Clearly the Markov chain $\{Q_n\}$ is irreducible and aperiodic. According to [2], A is a $\Delta_{r,r}$ -matrix and the ergodicity of $\{Q_n\}$ is given by the following criterion.

A. Lemma

Let $\{Q_n\}$ be an irreducible aperiodic Markov chain with the transition probability matrix A in the form of a $\Delta_{r,r}$ -matrix (1). $\{Q_n\}$ is recurrent positive iff

$$\lim_{z \rightarrow 1, z \in B(0,1)} \frac{d}{dz} A_i(z) < \infty, i = 0, 1, \dots, r-1 \quad (2)$$

And
$$\lim_{z \rightarrow 1, z \in B(0,1)} \frac{d}{dz} A_r(z) < r \quad (3)$$

Where $A_i(z)$ is the generating function of i th row of the transition probability matrix A and $B(z_0, \rho)$ denotes an open ball in \mathbb{C} centered at z_0 with radius ρ [2].

B. Proposition

The generating function $A_i(z)$ of i th row of the transition probability matrix A satisfies the following formula: $A_i(z) = \beta(\lambda - \lambda z) z^i G_i\left(\frac{1}{z}\right), i \in E$ (4)

$$\text{Where } G_i(z) = \begin{cases} \sum_{s=1}^i g_s z^s + \sum_{s=i}^r g_s z^i, & i < r \\ g(z) = \sum_{s=1}^r g_s z^s, & i \geq r \end{cases} \quad (5)$$

Proof:

Formulas (4) and (5) follow from (1) by use of standard probability calculus. Now we turn to Lemma 4.1. While condition (2) is obviously satisfied, formula (3) applied to (4) and (5) leads to the following.

C. Theorem

The imbedded Markov chain $\{Q_n\}$ is irreducible and aperiodic. It is recurrent positive if and only if $\rho < \bar{g}$ (6)

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where $\rho = \lambda b$ and $\bar{g} = E[c_1]$ is the mean server capacity.

V. INVARIANT PROBABILITY MEASURE

Given the equilibrium condition (6), the invariant probability measure $P = (p_i; i \in E)$ of the operator A exists and equals the stationary distribution of the Markov chain $\{Q_n\}$. The following statement obviously holds true.

A. Lemma

Let $P(z)$ denote the generating function of the invariant probability measure P of a transition probability matrix A of a homogeneous Markov chain $\{Q_n\}$, and let $A_i(z)$ denote the generating function of i th row of A . Then

$$P(z) = \sum_{i \in E} A_i(z) p_i \quad (7)$$

Using lemma 5.1 and the ideas of the last two sections, we obtain the following main result

B. Theorem

Given the ergodicity condition in theorem 4.3, the generating function $P(z)$ of the stationary distribution of the imbedded queueing process $\{Q_n\}$, satisfies the following formula:

$$P(z) = \frac{\beta(\lambda - \lambda z) \sum_{i=0}^{r-1} p_i z^i \left[G_i\left(\frac{1}{z}\right) - g\left(\frac{1}{z}\right) \right]}{1 - g\left(\frac{1}{z}\right) \beta(\lambda - \lambda z)} \quad (8)$$

where G_i is defined in (5).

Although formula (8) contains r unknown probabilities, p_0, \dots, p_{r-1} they can be determined from an additional condition which yields relatively simple equations. The latter can be solved numerically.

C. Theorem

The probabilities p_0, \dots, p_{r-1} , satisfy the following system of linear equations:

$$\left[\sum_{i=0}^{r-1} p_i \frac{d^k}{dz^k} z^i \left[G_i\left(\frac{1}{z}\right) \beta(\lambda - \lambda z) - 1 \right] \right]_{z=z_s} = 0, \quad k = 0, \dots, k_s - 1, s = 1, \dots, S \quad (9)$$

$$\sum_{i=0}^{r-1} p_i \sum_{s=i+1}^r g_s (s - i) = \bar{g} - \rho \quad (10)$$

where G_i satisfies formula (5) and $\{z_s; s = 1, \dots, S\}$ is the set of roots of the function $z^r - \beta(\lambda - \lambda z) \sum_{k=1}^r g_k z^{r-k}$ inside the unit ball $B(0,1)$ with their multiplicities k_s , such that $\sum_{s=1}^S k_s = r - 1$. The system of equations (9)-(10) has a unique solution, p_0, \dots, p_{r-1} .

Proof:

Formula (8) can be rewritten in the form

$$\sum_{i=r}^{\infty} p_i z^{i-r} = \frac{\sum_{i=0}^{r-1} p_i z^i \left(G_i\left(\frac{1}{z}\right) \beta(\lambda - \lambda z) - 1 \right)}{z^r - \sum_{k=1}^r g_k z^{r-k} \beta(\lambda - \lambda z)}$$

The rest of the proof is similar to that of theorem 5.2 [1].

D. Definition And Notation

Let $\beta_i = E^i[t_1]$. This gives the expected length of the service cycle given that the initial queue length was equal to i . Let $\beta = (\beta_i; i \in E)^T$. Then the scalar product $P\beta$ gives the value of the mean service cycle of the system in the stationary mode. We wish to call the ratio of the mean service cycle $P\beta$ and the mean inter arrival time the capacity of the system. Thus the capacity of the system is defined as $\lambda P\beta$. Earlier we denoted the mean server capacity by \bar{g} . Observe that for the classical M/G/1 queue the capacity of the system is $\lambda b + p_0 = 1$, which coincides with server capacity. Below we show we have this remarkable property in our case also, when the system is in the equilibrium.

E. Proposition

Given the equilibrium condition, the capacity of the system $\lambda P\beta$ and server capacity \bar{g} are equal.

Proof:

Evaluating β_i we have $\beta_i = b + I_{\{0, \dots, r-1\}}(i) \sum_{s=i+1}^r \frac{1}{\lambda} (s - i) g_s$, where I_D is the indicator function of a set D . The statement follows from the last equation and formula (10).

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VI. ANALYSIS OF THE CONTINUOUS TIME PARAMETER PROCESS

From the discussion in previous sections and from definition 2.1, it follows that $\{\Omega, \mathcal{F}, (P^x)_{x \in E}, Q(t); t \geq 0\} \rightarrow (E, \mathfrak{B}(E))$ is a semi regenerative process with conditional regenerations at points $t_n, n = 0, 1, \dots, t_0 = 0$. $\{\Omega, \mathcal{F}, (P^x)_{x \in E}, (Q_n, t_n): (t); t \geq 0\} \rightarrow (E \times \mathbb{R}_+, \mathfrak{B}(E \times \mathbb{R}_+))$ is the associated Markov renewal process. Let $s(t)$ denote the corresponding semi Markov kernel. With a very mild restriction to the probability distribution function B , we can have that the elements of $s(t)$ are not step functions and thus we can have (Q_n, t_n) aperiodic. By proposition 5.5 the mean inter renewal time $P\beta$ of the Markov renewal process equals $\bar{g}/\lambda (< \infty)$. Therefore (See Definition 2.3), the Markov renewal process is ergodic given the condition $\rho < \bar{g}$. Let $K(t)$ be the semi regenerative kernel (See Definition 2.4). The following proposition holds true.

A. Proposition

The semi regenerative kernel satisfies the following formulas:

$$K_{jk}(t) = \begin{cases} \sum_{s=j+1}^{\min(k,r)} K_{jk}^{(s)}(t)g_s + \pi_{\lambda t}(k-j)[1-B(t)]\sum_{s=1}^{\min(j,r)} g_s + \pi_{\lambda t}(k-j)\sum_{s=k+1}^r g_s, & 0 \leq j \leq k \\ 0, & 0 \leq k < j \end{cases} \quad (11)$$

Where $K_{jk}^{(s)} = \int_0^t e_{\lambda, s-j}(t-u)\pi_{\lambda u}(k-s)[1-B(u)]du, 0 \leq j \leq s-1, 1 \leq s \leq \min(k, r)$, (12)

While $(\pi_u; u \in \mathbb{R}_+)$ denotes the Poisson semi group and $e_{\lambda, k}$ is a k - Erlang probability density function with parameter λ .

Proof:

The statement follows from probability arguments. Now we are ready to apply the Main Convergence Theorem to the semi regenerative kernel in the form of corollary 2.6.

B. Theorem

Given the equilibrium condition $\rho < \bar{g}$ for the imbedded process $\{Q_n\}$, the stationary distribution $\pi = (\pi_x; x \in E)$ of the queueing process $\{Q(t)\}$ exists; it is independent of any initial distribution and is expressed in terms of the generating function $\pi(z)$ of π in the following formula:

$$\pi(z)\bar{g}(1-z) = P(z)[1-\beta(\lambda-\lambda z)] + \sum_{i=0}^{r-1}[G_i(z) - g(z)]p_i \quad (13)$$

where $P(z)$ is the generating function of P and G_i is defined in (5).

Proof:

Recall that the Markov renewal process (Q_n, t_n) is ergodic if $\rho < \bar{g}$. By corollary 2.6 the semi regenerative process $\{Q(t)\}$ has a unique stationary distribution π provided $\rho < \bar{g}$. From (11) and (12) we can see that the semi regenerative kernel is Riemann integrable over \mathbb{R}_+ . Thus following corollary 2.6 we need to find the integrated semi regenerative kernel H and then generating functions $h_j(z)$ of all rows of H . We have

$$\lambda(1-z)h_j(z) = [1-\beta(\lambda-\lambda z)]\{z^j\sum_{s=1}^j g_s + \sum_{s=j+1}^r g_s z^s\} + \sum_{s=j+1}^r g_s(z^j - z^s), 0 \leq j < r \quad (14)$$

$$\lambda(1-z)h_j(z) = z^j[1-\beta(\lambda-\lambda z)], r \leq j \quad (15)$$

Formula (13) now follows from proposition 5.5, formula (2.6) and expressions (14) and (15).

VII. EXAMPLE

We studied 13 healthy subjects (9 Male / 4 Female) and 6 patients (3 Male / 3 Female) with T2DM. None of the healthy subjects had a family history of diabetes or other endocrine disorders or were taking medications. The patients with T2DM were treated with long-acting insulin (3/6), short acting insulin (2/6), sulfonylureas (2/6), metformin (5/6), blood pressure lowering drugs (5/6), and lipid lowering drugs (4/6). All drugs except insulin were discontinued 2 days before admission. The last insulin dose was taken 2 h before admission. Body weight of all study volunteers was stable for at least 2 months before the studies. The following three studies were performed.

Study 1: 8 Hour Hyperglycemic Hyperinsulinemic (No Insulin Infusion) Clamps in Healthy Subjects (n = 6)

Study 2: 8 Hour Hyperglycemic Hyperinsulinemic (No Insulin Infusion) Clamps With Coinfusion of Lipid/Heparin in Healthy Subjects (n = 7)

Study 3: 8 Hour Isoglycemic Hyperinsulinemic (Insulin Infusion at a Rate of 2 mU/kg/min) Clamps in 6 Patients With T2DM

Plasma glucose was measured with a glucose analyzer. Insulin was determined in serum by radioimmunoassay with a specific

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antibody that cross-reacts minimally (0.2%) with proinsulin. Free fatty acids (FFAs) were measured in plasma, containing Paraoxon, a lipoprotein lipase inhibitor, with a kit from Wako Pure Chemical. Infusion of glucose, either without or with infusion of lipid in healthy subjects (Studies 1 and 2), final resulted in similar degrees of hyperglycemia and hyperinsulinemia but different levels of plasma FFA {Figure (1)} [15], [16] & [17].

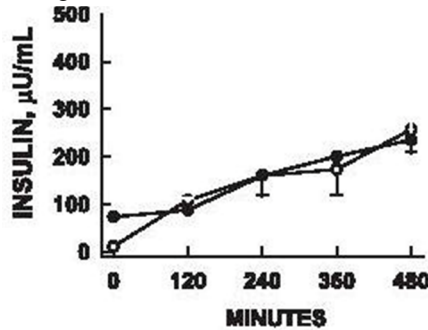


Figure (1): Effects of Lipid Induced Insulin Resistance on UPR mRNA

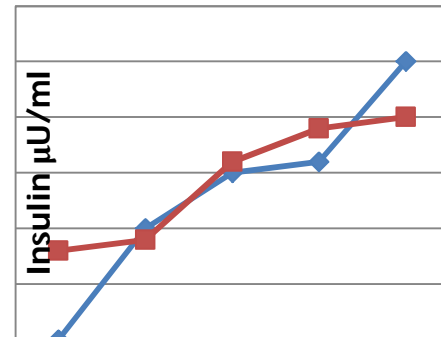


Figure (2): Effects of Lipid Induced Insulin Resistance on UPR mRNA Using Normal Distribution

VIII. CONCLUSION

The lipid infusions produced acute insulin resistance and diminished insulin mediated ER stress responses in adipose tissue of normal subjects and that insulin was unable to increase ER stress responses in chronically insulin-resistant patients with T2DM. There is no significance difference between medical and mathematical reports using normal distribution. The medical reports are beautifully fitted with the mathematical model. Hence the mathematical report {Figure (2)} is coincide with the medical report {Figure (1)}.

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