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RESEARCH ARTICLE

STOCHASTIC MODEL TO ESTIMATE THE CHANGES IN PLASMA INSULIN AND FFAS DURING OLTT AND OGTT USING NORMAL DISTRIBUTION

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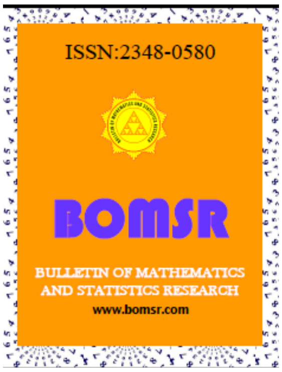

ABSTRACT

Elevated plasma free fatty acids (FFAs) are one important link between excess visceral adiposity, insulin resistance, and the development of type 2 diabetes. Effects of lifestyle interventions on FFA metabolism are poorly known. This open-label study was conducted to test the effects of a one year healthy eating/physical activity intervention program on plasma FFA homeostasis in 117 viscerally obese men with dyslipidemia associated with insulin resistance. In this paper, we calculate the changes in plasma insulin and plasma FFAs during OLTT and OGIT with the help of single buffer multiclass queue.

Key Words: Insulin, Free Fatty Acids, OLTT, OGIT, Multiclass Queue & Normal Distribution

1. INTRODUCTION

Excess visceral adiposity has been associated with deteriorated cardiometabolic risk profile and increased risk of developing type 2 diabetes and cardiovascular diseases [5] & [10]. In both fasting and postprandial conditions [14], obese patients have increased concentrations of plasma free fatty acids (FFAs) compared with lean patients [2] & [13]. Although visceral adiposity lipolysis accounts for less than 20% of systemic circulating FFA in obese patients, these FFAs are released directly into the portal vein, thereby exposing the liver to more FFA than would be predicted from systemic FFA [13]. Moreover, in vitro studies have shown that visceral adipocytes are characterized by increased lipolysis compared with subcutaneous adipocytes [11] because visceral fat is much less sensitive to lipolysis inhibition by insulin than subcutaneous fat [12]. Thus, increased visceral fat increases delivery of deleterious levels of FFA to the liver via the portal vein, leading to elevated hepatic triglyceride concentration and hepatic insulin resistance. Therefore, abdominal adiposity is an important determinant of postprandial plasma FFA flux. Increased plasma FFA, especially in the postprandial state, seems to be one important link between excess visceral adiposity; ectopic fat deposition, insulin resistance, and the development of type 2 diabetes [3].

Few studies have addressed the effect of lifestyle intervention on FFA homeostasis, particularly in relation to changes in visceral adiposity. An ancillary study from the Look AHEAD trial was conducted in obese patients with type 2 diabetes who participated to the intensive lifestyle intervention arm. In this study, assessed insulin sensitivity and FFAs during a hyperinsulinemic euglycemic clamp in 26 men and 32 women. One year of intensive lifestyle intervention elicited an increase in exogenous insulin mediated glucose uptake as well as a decrease in FFA concentrations during the clamp, demonstrating improved insulin sensitivity of both glucose metabolism and lipolysis inhibition. Furthermore, [6] performed a study of 19 obese patients with impaired glucose tolerance to evaluate the effects of 4 weeks of aerobic exercise training on fat distribution and metabolism.

In this paper, we consider a single-buffer multiclass queue. We consider two cases separately: fluid queue and ordinary queue. In the fluid case the input to the queue is fluid that belongs to K different type's modulated K independent Markovian on-off processes. The k^{th} $(k = 1,2, \dots, K)$modulating process on for an $\exp\ (\mu_k)$ amount of time and off for an $\exp\ (\lambda_k)$ amount of time. When it is on, the fluid of type k arrives at rate $r_k > 0$, and no fluid arrives while it is off. Thus the input process of type k is completely described by three parameters: (λ_k, μ_k, r_k). The fluid belonging to all classes accumulates in a single buffer and is removed on a first come first served (FCFS) basis. In a fluid setting, the FCFS discipline is taken to mean that fluid arriving at time t is removed from the buffer only after will be processing fluids of many types simultaneously. The output from such a queue is rather complex. We show that the case of a two-class system. The output processes of different types of fluids are neither independent, nor can be described by three-parameter on-off processes. Our aim is to approximate the output process of type k fluid by three-parameter on-off process with parameters $(\lambda_k^{\circ}, \mu_k^{\circ}, r_k^{\circ}), k = 1,2, \dots K$.

One motivation behind this analysis is in telecommunication networks. The idea of using fluid queues in telecommunications is well established, initiated by the pioneering work by [1]. There is a large literature on fluid queues; wee the survey paper by [1]. Several researchers have also studied networks of fluid queues: see [7] & [8]. Exact analysis of fluid networks is intractable, and hence we need to find methods of approximate analysis. In this regard, earlier work done in queueing networks is a valuable guide. One promising approach is the decomposition approach, as presented by [1] and further refined by [15] in QNA. A similar approach is also considered by [9] & [4]**.** The idea is to model the telecommunication network as a network of multiclass fluid queues with FCFS discipline at all nodes. Here we assume that the external fluid inputs to all the nodes in the network are Markovian on-off processes described by three parameters. Then we approximate the output processes from a given node as independent Markovian on-off processes by using the methodology developed here. That is, we think of a node as a non linear mapping of the input to other queues. We seek an equilibrium solution to the nonlinear system where the output parameters are consistent with the input parameters.

It is clear that the results here will be impractical to use for large values of K since the distributions involve matrices of size 2^K. We will develop computationally efficient approximations for computing the output parameters distribution of the input parameters. The results developed here can be used to quantify the case of these approximations. This work is under progress and will be reported at a later case of the ordinary queue is the standard M/G/1 queue with multiple types of customers. Customers belong to K different types and arrive according to K independent Poisson process. The arrival rates and service time distributions are class-dependent. The service time is FCFS. The output analysis of this queue is given in the next section.

2. Output analysis:

Accomplish the aim of characterizing the output of fluid type k as a three-parameter on-off times, we define the output process of type k to be 'on' if fluid of type k is emerging from the fluid at a positive rate, and 'off' if no fluid of type k is emerging from the buffer. The distributions of the on and off times of the output process of type k are complicated. Let τ_k^{on} and τ_k^{off} denote their respective means. Then we approximate the output on and off times exponential random variables with parameters

$$\lambda_k^{o} = \frac{1}{\tau_k^{\text{off}}} \tag{1}$$

$$\mu_k^{o} = \frac{1}{\tau_k^{\text{on}}} \tag{2}$$

The actual rate at which fluid of type k emerges during the on time of the output process of type differences. The mean input rate of fluid of type k is given by

$$m_k = r_k \frac{\lambda_k}{\lambda_k + \mu_k}$$

It is known that (See [9]) the fluid queue is stable if

$$m = \sum_{k=1}^{K} m_k < c$$

In a stable system, the mean output rate m_k^0 of type k fluid must be the same as its mean input on time. Hence, if we approximate the output rate during the output on time by a constant r_k^0 (which we call the effective peak rate of the output process), we must have

$$m_k^{o} = r_k^{o} \frac{\lambda_k^{o}}{\lambda_k^{o} + \mu_k^{o}} = m_k$$

Using (1) and (2) we get

$$r_k^{o} = r_k \frac{\lambda_k}{\lambda_k + \mu_k} \frac{\tau_k^{\text{on}} + \tau_k^{\text{off}}}{\tau_k^{\text{on}}} \tag{3}$$

Equations (1) to (3) imply that the output process of type k can be approximated by an on-off processes with parameters $(\lambda_k^{o}, \mu_k^{o}, r_k^{o})$ if we know the mean output on time τ_k^{on} and the mean off time τ_k^{off}.

3. Multiclass M/G/1 Queue:

Consider a single-server queue with K classes of customer. Customers of class $k(1 \le k \le K)$ arrive according to a Poisson process with rate λ_k and form a single line. They are served by a single server according to a first come first served discipline. The service times of a class k customers are i.i.d with mean ν_k. The classes are independent of each other. A multiclass M/G/1 queue with an FCFS service discipline may be regarded as a standard single-class M/G/1 queue arrival rate

$$\lambda = \sum_{k=1}^{K} \lambda_k \tag{4}$$

And mean service time

$$\nu = \sum_{k=1}^{K} \frac{\lambda_k \nu_k}{\lambda} \quad (5)$$

Let $\rho_k = \lambda_k \nu_k$ (6)

The queue is stable if

$$\rho = \sum_{k=1}^{K} \rho_k < 1 \quad (7)$$

Define $S(t)$ to be the state of he server as follows: $S(t) = 0$ if the server is idle at time t, and $S(t) = k$ if the server is serving a customer of class k at time t. Clearly the $\{S(t), t \geq 0\}$ process is a regenerative process with state space $\{0,1,2, \ldots \ldots, K\}$, and it regenerates whenever a enters state 0. In this section, we compute τ_k, the expected sojourn time in state k, and τ_{kk}, the expected inter visit time to state k. The main result is given in the following theorem.

3.1 Theorem:

Assume that the queue is stable. Then

$$\tau_k = \frac{\lambda \nu_k}{(1-\rho)\lambda_k + (\lambda - \lambda_k)}, \ 1 \leq k \leq K \quad (8)$$

And

$$\tau_{kk} = \frac{\lambda}{(1-\rho)\lambda_k^2 + \lambda_k(\lambda - \lambda_k)} = \frac{\tau_k}{\rho_k}, 1 \leq k \leq K \quad (9)$$

Proof:

Since the queue is assumed to be stable, ρ_k is the long-run fraction of the time the server is busy serving customers of class k. Suppose that $S(0) = 0$, and define T to be the first time the S process re-enters state 0. Furthermore, define T_k to be the total time spent in state k of the S process during $(0, T]$, and N_k to be the total number of visits to state k during $(0, T]$. Results from regenerative processes imply that

$$\rho_k = \frac{E(T_k)}{E(T)} \quad (10)$$

$$\tau_k = \frac{E(T_k)}{E(N_k)} \quad (11)$$

$$\tau_{kk} = \frac{E(T)}{E(N_k)} \quad (12)$$

Since $E(T)$ is the expected length of a busy cycle in an M/G/1 queue with arrival rate λ and mean service times ν as given in (4) and (5), we have

$$E(T) = \frac{1}{\lambda} + \frac{\nu}{1-\rho} = \frac{1}{\lambda(1-\rho)}$$

Where ρ is defined in (7). Using (10) **w**e get

$$E(T_k) = \frac{\rho_k}{\lambda(1-\rho)} \quad (13)$$

Where ρ_k is defined by (6).

Next we compute $E(N_k)$. Let N be the total number of customers served during the first busy cycle, and let X_n be the type of the n^{th} customer $(1 \leq n \leq N)$. The FCFS service discipline implies that

$$N_k = I\{X_1 = k\} + \sum_{n=2}^{N} I\{X_{n-1} \neq k, X_n = k\}$$

Hence,

$$E(N_k) = P(X_1 = k) + E\left(\sum_{n=2}^{N} I\{X_{n-1} \neq k, X_n = k\}\right)$$

Using the fact that $\{X_n, n \geq 1\}$ is a sequence of i.i.d random variables with common probability mass function

$$P(X_n = k) = \frac{\lambda_k}{\lambda}\ , 1 \leq k \leq K$$

We get

$$E(N_k) = \frac{\lambda_k}{\lambda} + \{E(N) - 1\}\frac{\lambda_k}{\lambda}\left(1 - \frac{\lambda_k}{\lambda}\right)$$

From the results for a standard M/G/1 queue, we know that $E(N) = 1/(1-\rho)$. Using this we get

$$E(N_k) = \frac{\lambda_k^2}{\lambda^2} + \left(\frac{1}{1-\rho}\right)\left(\frac{\lambda_k}{\lambda}\right)\left(1 - \frac{\lambda_k}{\lambda}\right) \quad (14)$$

Using (14) and (13) in (11) and (12) we get (8) and (9).

This completes the proof.

4. Example:

Caucasian men (n=144) between the ages of 30 and 65, with abdominal obesity, elevated triglyceride concentrations (1.69 mmol/L), low HDL cholesterol (1.03 mmol/L), or all three, were recruited by media solicitation to participate in an open-label, uncontrolled, 1-year intensive lifestyle modification program with 3 years of follow up. This study focuses on the results after 1 year in the 117 men that completed the first year of intervention. Subjects dropped out mainly because of an inability of some participants to attend the regular follow-up visits planned with the study dietitians and kinesiologist. Subjects with type 2 diabetes, with BMI values 25 or 0.40 kg/m2, or those taking medication targeting glucose, lipid metabolism, or blood pressure (BP) management were excluded. Four patients developed type 2 diabetes after 1 year [11]. Diabetes was diagnosed by the 1-year oral glucose tolerance test (OGTT) and oral lipid tolerance test (OLTT). Thus, subjects did not take any antidiabetic medications during the follow-up period of the current study. Subjects were counseled individually once every 2 weeks during the first 4 months of the study, with subsequent monthly visits to improve their nutritional and physical activity/exercise habits. Each visit included an interactive session with a registered dietitian followed by a meeting with a kinesiologist. The nutritional counseling was personally adapted to elicit a 500-kcal daily energy deficit, including less than 30% of kilocalories from lipids, preferably unsaturated. The daily caloric intake was estimated at baseline and at year 1 by a 3-day dietary record including one nonworking day. The aim of the physical activity program was 160 min/week of moderate-intensity endurance exercise. Men received a personalized training program that was adapted according to subjects' history, preferences, maximal treadmill test results, and the ratings of their self-perceived exhaustion [14]. Based on results, plasma insulin concentrations following the oral lipid load were significantly lower after 1 year of intervention (Figure 1).

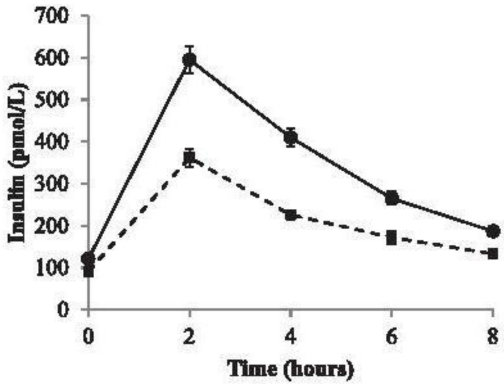

Figure (1): Changes in plasma insulin and plasma FFAs during OLTT and OGTT.

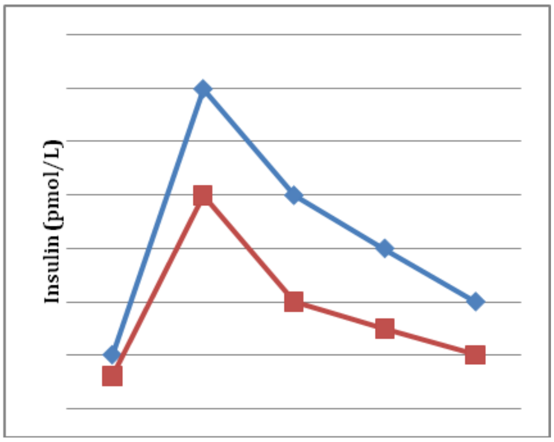

Figure (2): Changes in plasma insulin and plasma FFAs during OLTT and OGTT using Normal Distribution.

5. Conclusion

One year healthy eating/physical activity intervention improved the suppression of FFAs after oral glucose and lipid load tests in viscerally obese men, possibly due to improved responsiveness to insulin. This insulin mediated regulation of postprandial plasma FFA levels could be a link between visceral obesity and impaired glucose homeostasis. Single buffer multiclass queue by using 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)}.

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