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An Application of Queueing Theory to the Relationship Between Insulin Level and Number of Insulin Receptors

[Kuyruk Kuramının İnsülin Düzeyi ve İnsülin Reseptörleri Sayısı Arasındaki İlişkiye Uygulanması]

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ABSTRACT

Insulin is a hormone that regulates blood glucose levels. Its deficiency or over secretion cause many disorders including polyurea, polydipsia, and weight loss in metabolism. Publications to date show strict relationships between insulin level and number of insulin receptors in a cell. In this respect a mathematical estimation on insulin level and number of insulin receptors may be important in order to understand some diseases related to insulin level and number of insulin receptors. In the present study, a queueing theory originated model is applied to insulin level and number of insulin receptors. Based on real data, some parameters such as optimum insulin level, number of insulin receptor and minimum required energy spent were calculated by using queueing theory. Our results show an indirect correlation between insulin level and receptor. The total energy spent is also decreased up to optimum number of insulin receptors and then it is increased. From the results, it could be said that queuing theory predicts the optimal number of insulin receptors. In conclusion, the data reveals that queueing theory can be applied to insulin level and number of insulin receptors. Estimation of insulin levels in insulin-insulin receptor complex and number of insulin receptors obtained through queueing analysis may identify etiological origins of some insulin-based metabolic disorders.

Key Words: Arrival rate, insulin, number of insulin receptors, queueing, service rate, human metabolism.

ÖZET

İnsülin kan glukoz düzeylerini regüle eden vücut hormonlarından birisidir. Eksikliği veya aşırı sekresyonu poliüre, polidipsia ve kilo kaybı gibi birçok rahatsızlıklara neden olur. Günümüze kadar insülin üzerine yapılan çalışmalara göre hücrelerde insülin düzeyi ve insülin reseptör sayısı arasında bir ilişki bulunmaktadır. Bu açıdan bakıldığında matematiksel yöntemlerle insülin düzeyi ve insülin reseptör sayısı ilişkinin ifade edilmesi insülin düzeyi ve insülin reseptör sayısına yönelik bazı metabolik rahatsızlıkların anlaşılmasında önem arzedebilir. Sunulan çalışmada kuyruk kuramı kökenli bir model insülin düzeyi ve insülin reseptör sayısı arasındaki ilişkiye uygulanmıştır. Gerçek veriler kullanılarak, optimum insülin düzeyi, insülin reseptör sayısı ve harcanması gereken minimum enerji düzeyi kuyruk kuramı ile ifade edilmiştir. Sonuçlara göre, insülin reseptör sayısı arttıkça, sistemde bulunan insülin düzeyi azalmaktadır. Toplam harcanan enerji de optimum insülin reseptör sayısına kadar azalmakta ve daha sonra artışlar gözlenmektedir. Sonuçlara göre kuyruk kuramıyla optimum insülin reseptör sayısının tahmin edilebileceği görülmektedir. Kuyruk kuramı insülin düzeyi ve insülin reseptör sayısı arasındaki ilişkinin açıklanmasında alternatif bir yaklaşım olabilir. İnsülin düzeyi ve insülin reseptör sayısının kuyruk kuramı ile tahmin edilmesi bazı insülin tabanlı metabolik hastalıkların etiyolojisinin anlaşılmasında kullanılabilir bir yaklaşım olabileceği görülmektedir.

Anahtar Kelimeler: Geliş oranı, insülin, insülin reseptörleri, kuyruk kuramı, servis oranı, insan metabolizması

INTRODUCTION

Insulin is one of the important hormones that regulates the glucose level in blood. Insulin in body is secreted by islets of Langerhands in pancreas. Insulin, a peptide based hormone, was first purified, then crystallized and has been subsequently synthesized chemically and biotechnologically. Insulin is made up of two polypeptide chains which are called A (or α) and B (or β). There are two inter- and one intra- disulphide bridges in one insulin molecule. The insulin level is of paramount importance in carbohydrate, lipid and protein metabolism. Its deficiency causes increased gluconeogenesis. Polyurea, polydipsia, and weight loss are the major symptoms of insulin deficiency (1).

Several mathematical models have been developed to study insulin. De Gaetano and Arino (2000) discussed the minimal model on glucose-insulin plasma concentrations following the intravenous glucose tolerance test and they introduced a simple delay-differential model for comparison (2). Doran et al. (2004) developed a derivative weighted active insulin control model for intensive care unit patients (3). Mari (1998) also developed a modelling analysis for assessing insulin sensitivity with a tracer-modified intravenous glucose tolerance test (4). When insulin interacts with the active site of insulin receptor, some conformational changes occur and finally high glucose level in blood is decreased via gluconeogenesis. Unfortunately, five percent of the population in even developed countries is suffering from a disorder in biosynthesis of insulin which is called "Diabetes mellitus" (1). Due to above mentioned events in body, studies on the insulin biosynthesis and its actions might be of importance in the understanding of diabetes mellitus.

In recent years, application of stochastic methods has been increased in analyzing clinical problems. Especially queueing theory has been applied to the study of various physiological problems (5). By this way, one can reveal a measure of organ (or sub-organ) function (6).

Queueing theory, as the most common application of the stochastic process, examines queues or waiting lines dealing with random input and servicing processes (7). The queues form, when the demand for a service exceeds its supply. Queue affects adversely the important parameters such as cost and time. Number of servers, customers and their arrival rate to the system are important parameters of queueing theory. There are several types of queue models which are classified by the number of server, the distribution of arrival process etc (8).

Optimization of both energy use in living systems and the cost in servicing systems in real life is of great importance. The failure in the optimization of both systems results with death and bankrupcy, respectively. The billion-year evolutionary process has resulted in the optimization of energy used in the living systems. Therefore, excellent cost (or energy) and manufacturing (or synthesis) relation can be easily observed in living systems. Histidin and Lac operon in some bacteria could be good examples for the latter one. There is no reason not to apply this excellent relation to realize in our life in some cases such as cashiers in supermarkets, servers in motorways and ticket offices etc. On the other hand, understanding of optimization process and factors that affect the optimum queue system in living things can help us clarify ethiological factors of some diseases. so far there have been many efforts on this topic (5-7,9,10).

In the present study, applicability of queueing theory, Markov/Markov/c (M/M/c) queue model, for explanation of the relationship between insulin level and number of insulin receptors has been investigated. Because cells have ability to change numbers and activity of insulin receptors, we aimed at the use of queuing theory to find optimum number of insulin receptors and bring up the concept of metabolic energy balance and optimal energy use. According to our literature search, no published material existed on the use of queueing theory on the relationship between insulin level and number of insulin receptors.

MODEL

The M/M/c queue is a model with a parameter $1/\lambda$ inter-arrival time and the service time of which has a parameter $1/\mu$ exponential distribution. The arrival rate does not depend on the number of customers in the system. The way the queue is organised is that the system has c servers and uses FCFS (First-come, First-served) service discipline. The space for the waiting line is infinite size (11). This model is based on the basic birth-death process as shown in Figure 1 (12).

The study of queues determines the measures of performance of queueing systems, including the average waiting time and the average queue length (8). This information is then used by managers to decide on an appropriate level of service for the facility. The basic objective in most queueing models is to achieve a balance between two costs; cost of offering the service and cost of delay in offering the service. The optimum number of server to reach the minimum cost (12) must be identified as illustrated in Figure 2. Cost or in other words, energy is an important value in living systems. As far as we know that the use of energy in living systems is excellent, it might be of great importance to express these events mathematically. In this study, cost, number of servers, customers, their arrival rate and service rate correspond to energy value, number of insulin receptors, insulin level and arrival rate of insulin per unit time and insulin-insulin receptor complex per unit time, respectively. Figure 3 shows how the relation between insulin and insulin receptor can be investigated in terms of the queueing systems. Thus, in the present study, a novel mathematical approach on the relationship between insulin level and number of insulin receptors was investigated by using queueing theory.

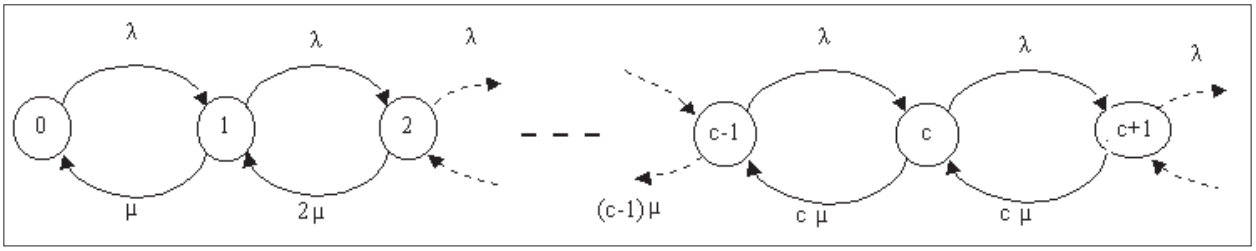

Figure 1. The transition rate diagram for the M/M/c queue (12)

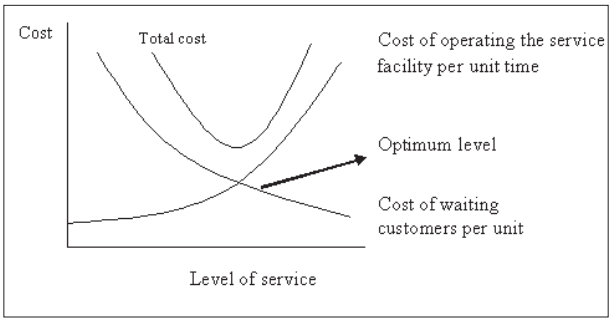

Figure 2. Costs of Queueing Systems (12)

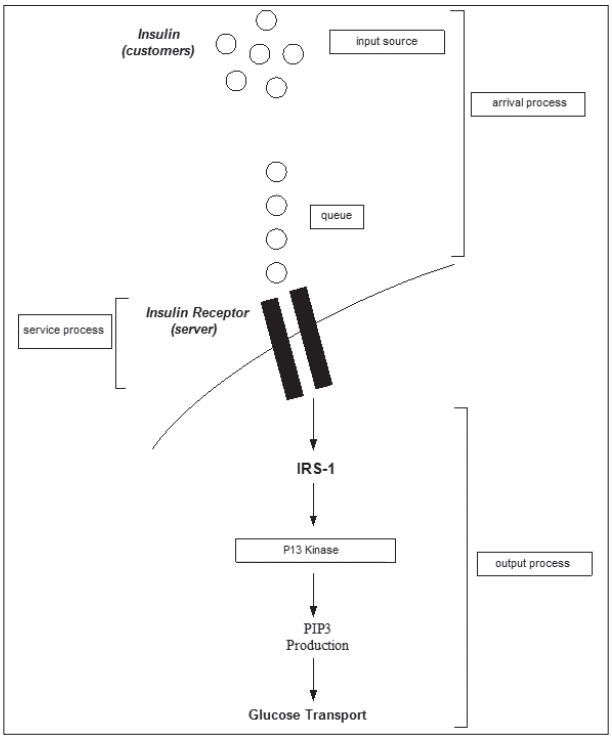

Figure 3. Schematic diagram of investigating insulin and insulin receptor as a queueing system

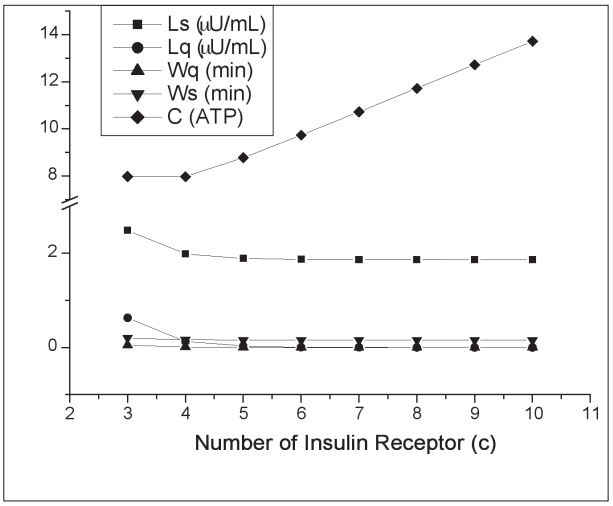

Figure 4. The relationships between number of insulin receptor (c) and expected amount of insulin in system (Ls), insulin number in queue (Lq), waiting time in queue (Wq), waiting time in the system (Ws) and and total energy spent (C)

PROCEDURES OF PARAMETERS ESTIMATION

The parameters used in the present study were defined as follows (8):

λ : Arrival rate of insulin level per unit time (μU/mL.min)

μ : Insulin-insulin receptor complex per unit time (μU/mL.min)

c : Number of insulin receptors (103 receptors/red cell)

Lq : Expected amount of insulin level in queue (μU/mL)

Ls : Expected amount of insulin level in system (μU/mL)

Wq : Waiting time of insulin to interact with its receptor in queue (min.).

Ws : Total waiting time of insulin to interact and react with its receptor in system (min.)

Wservice: Reaction time in the system (min.)

C1 : Spent energy value for insulin-insulin receptor complex (ATP)

C2 : Energy gap in the case of over production of insulin (ATP)

C : Total spent energy for insulin-insulin receptor complex (ATP)

As was defined above cost, number of servers, customers, their arrival rate and service rate correspond respectively to energy value (combination of energy spent value for insulin-insulin receptor complex, energy gap in the case of over production of insulin, and total energy spent for insulin-insulin receptor complex), number of insulin receptors, insulin level and arrival rate of insulin

per unit time and insulin-insulin receptor complex per unit time in the present study. Wq and Ws are of also important paremeters in our model since these parameters are also associated with some of the inputs of queueing theory. System is expressed as insulin-insulin receptor complex in the present study. λ and μ are assumed to be exponentially distributed.

Since c parallel receptor numbers (servers) exist in the systems, the service rate (μ) of the system is expressed as $n\mu$ if $n \le c$ and $c\mu$ if $n > c$ which is illustrated in Fig. 1.

Let x=c represent the number of receptors.

Model of energy spent can be expressed as follows:

$$E(C_T(x)) = E(C_O(x)) + E(C_W(x)) \quad (1)$$

where

$E(C_T(x))$: Expected total energy spent per insulin receptor.

$E(C_O(x))$: Expected spent energy value for insulin-insulin receptor complex per insulin receptor.

$E(C_W(x))$: Expected energy gap in the case of over production of insulin per unit time.

Eq. (1) can be simplified (8) as follows.

$$C = C1.c + C2.Ls \quad (2)$$

As can be seen above, c is expressed as number of insulin receptors. To calculate the total energy spent (C), value for the interaction between insulin and insulin receptor, c is multiplied with C1. On the other hand, this value is not sufficient to express total energy value because under some conditions (e.g disorders, diseases) insulin is over-secreted and this situation increases total energy spent or, in other words, the cost is increased. Therefore, such extraordinary situations are also considered by the formula (2). In the present study, 1 ATP and 2 ATP are assumed respectively as energy spent for one insulin molecule per insulin receptor (C1) and energy spent for over secretions of insulins (insulin molecules in the queue) (C2).

$$L_s = L_q + \rho \quad (3)$$

In Eq. (3), we defined Lq and Ls as follows,

ρ : is expressed as $\frac{\lambda}{c\mu}$ (which is defined as insulin-insulin receptor complex utilization factor)

where

$$L_q = \frac{\rho^{c+1}}{(c-1)!(c-\rho)^2} p_0 \quad (4)$$

In order to obtain p0 (probability of no insulin level in the receptor), following Eq. (5) is required,

$$p_n = \begin{cases} \frac{\lambda^n}{\mu(2\mu)(3\mu)\ldots(n\mu)} p_0 = \frac{\lambda^n}{n!\mu^n} p_0 & n \le c \\ \frac{\lambda^n}{\mu(2\mu)\ldots(c-1)\mu(c\mu)^{n-c+1}} p_0 = \frac{\lambda^n}{c!c^{n-c}\mu^n} p_0 & n > c \end{cases} \quad (5)$$

Where

p_n : Probability that n insulin exist in the system.

$$p_0 = \left\{ \sum_{n=0}^{c-1} \frac{\rho^n}{n!} + \frac{\rho^c}{c!} \left(\frac{1}{1-\frac{\rho}{c}} \right) \right\}^{-1}, \qquad \frac{\rho}{c} < 1 \quad (6)$$

Additionally Wq and Ws could be determined as follows,

$$W_q = L_q / \lambda \quad (7)$$

$$W_s = L_s / \lambda \quad (8)$$

$$W_s = W_q + W_{service} \quad (9)$$

In the present study, C, c and Lq, Ls, Wq, Ws values were calculated by using TORA software.

RESULTS

In this study, λ and μ were taken as 12.3 μU/mL min and 6.6 μU/mL. min, respectively. These values were obtained from Table 1 which was retrieved from a table on glucose-insulin kinetic (13,14). λ and μ rates were calculated in the increases and decreases of insulin level in the time period between 0-6 min and 6-12 min, respectively. Total spent energy (C, expressed as ATP), the number of receptors (c, 103 receptors/red cell), expected amount of insulin level in system (Ls, expressed as μU/mL), expected amount of insulin level in queue (Lq, expressed as μU/mL), waiting time in system (Ws, expressed as min.) and waiting time in queue (Wq, expressed as min.) were calculated by TORA software programme. The results obtained are presented in Figure 4.

As can be seen from Figure 4, a sharp decrease in Ls value was observed at 5th insulin receptor number then Ls values remained constant. The Ls values in 4th and 5th receptors were 1.99 and 1.89, respectively. After 6th receptor, the Ls values were approximately close (6, 1.87 μU/mL), (7, 1.86 μU/mL), (8, 1.86 μU/mL), (9, 1.86 μU/mL). When the values are examined, it can be seen that when the insulin level is decreased, receptor number is increased.

Figure 4 showed that after 7th insulin receptor numbers, Lq values were unchanged and it was zero. As the number of insulin receptor (c) gave service to all incoming

Table 1. Insulin kinetics values (13,14)

Time (min)	Insulin level (μU/ml)
0	11
2	26
4	130
6	85
8	51
10	49
12	45

insulin levels, the number of insulin level in queue (Lq) went to zero. The Lq values were (4, 0.124 μU/mL), (5, 0.027 μU/mL), (6, 0.005 μU/mL), (7, 0.001 μU/mL), (8, 0.00 μU/mL), (9, 0.00 μU/mL), (10, 0.00 μU/mL).

The relationship between insulin receptor numbers (c) and waiting time in queue (Wq) was also presented in Fig. 4. If the number of insulin receptor (c) is increased, the waiting time of insulin level in queue (Wq) is decreased. The Wq values were (4, 0.01 min.), (5, 0.002 min.), (6, 0.000 min.), (7, 0.000 min.), (8, 0.000 min.), (9, 0.000 min.), (10, 0.000 min.).

According to Fig. 4, if the number of insulin receptor (c) is increased, waiting time of the insulin level in the system is decreased. The Ws values were (4, 0.161 min.), (5, 0.153 min.), (6, 0.152 min.), (7, 0.151 min.), (8, 0.151 min.), (9, 0.151 min.), (10, 0.151 min.). As it can be seen from Eq. (9), when the number of insulin receptor is 7 or more, the values of waiting time in the system (0.151 min.) is the same as the service time in the queueing system. Insulin does not spend any time in queue after 7th insulin receptor.

Fig. 4 also shows the relationship between total energy spent for insulin-insulin receptor (C) and the number of insulin receptors (c). According to Fig. 4, the total energy spent is decreased up to optimum number of insulin receptor and then it is increased. The C values versus c were (2, 30.3 ATP), (3, 7.98 ATP), (4, 7.97 ATP), (5, 8.78 ATP), (6, 9.74 ATP), (7, 10.73 ATP), (8, 11.73 ATP), (9, 12.73 ATP), (10, 13.73 ATP). As can be seen from data, the minimum total spent energy was observed in 4th insulin receptor as 7.97 ATP.

DISCUSSION

Queueing theory was first postulated for studying queueing phenomena in commerce, telephone traffic, transportation, business-industrial servicing etc (15). Applicability of mathematical and statistical models to human metabolism have been published (5-7,9,10,16). In the present study, in the existence of different number of insulin receptors, some important parameters such as λ (arrival rate of insulin per unit of time), μ (insulin-insulin receptor complex per unit of time), Ls (expected amount of insulin level in system), Lq (expected amount of insulin level in queue), c (number of insulin receptors), Ws (waiting time in system), Wq (waiting time in queue) and C (total spent energy) were examined and evaluated. As was mentioned in many fundamental papers on queueing theory, cost is an important value in this theory. Cost is equal to energy value in our hypothesis. In human metabolism, use of energy is important. A malfunction in energy metabolism causes remarkable disorders in body. Therefore, approaches of energy use in human metabolism may be mimicked in daily life, particularly in industry. The optimum insulin receptor number was found 4 because of the observation of lowest energy value in this point. In the other insulin receptor numbers, remarkable increased energy values compared to point 4 were observed. In addition, after 4th insulin receptor number, Ls values were quite similar (Figure 4). When Lq values were approximately zero as was shown in Fig 4, it could be said that when number of insulin receptor was 4, all secreted insulin molecules would be in the service process. Up to 4th insulin receptor number, a sharp decrease was observed in Wq levels; however, waiting time in queue (Wq) levels were going down and approximately close to zero after 4th insulin receptor number. In the case that insulin receptor is 4; all secreted insulin goes to service to bind receptors. Therefore, the condition where energy spent minimum equals to the condition where number of receptor is 4 (Figure 4). When number of insulin receptors increases the energy spent for insulin-insulin receptor complex also increases. At the same time, energy gap by over production of insulin decreases. In order to find minimum energy spent intersection point of used energy value for insulin-insulin receptor complex (cost of operating the service facility per unit of time in Figure 2) and energy gap in the case of over production of insulin (cost of waiting customers per unit time in Figure 2.) is evaluated (12). By using these data, both minimum waiting time in queue and minimum cost are obtained for the optimal insulin receptor number. The analyses of real life queues from our daily life such as motorway servers, supermarket cashiers, and so on, could be applied to human systems.

There are a few papers on the relationship between queueing theory and human metabolism in the literature. Wu (1998) investigated applicability of queueing theory with Monte Carlo simulation on effects of ethanol (7). In this paper, the accumulated adverse effects of ethanol in the body and the time required for removing the adverse effects of ethanol in the body was estimated by using the queueing theory. In this paper, the minimization of requirement for detailed information on the anatomical structure in the use of queueing theory has also been argued. Wu (1998) in his paper has used M/M/1 model to apply queueing theory and we used multiserver queue model in our study, M/M/c, both models have interarrival time which are exponentially distributed with parameter 1/λ and service times which are exponentially distributed with parameter 1/μ. And both models Wu's and ours use FCFS service discipline. However, Wu (1998) defined "body" as one system in his paper whereas in our study we examined multiserver queueing system. Because in real conditions, cells have lots of insulin receptors which are defined as servers in our study. While Wu (1998) has also applied Monte Carlo simulation to easily produce discrete data, real life data has been applied in our study (10).

Wu (1998) in his study, examined respiratory system dealing with inhaled toxicants as a queueing system in which the amount of toxicants in the respiratory system and the time needed to remove the accumulated amount of toxicants from respiratory system were correlated to or associated with the number of customers and avarage

waiting time in the servicing system respectively (7,10). In latter paper, M/M/1 queue model has also been used with Monte Carlo simulation.

Schell (1994) has presented a queueing model for cholesterol and has introduced a two-sided ballot theorem (9). According to Schell's papers, all factors causing an increase and a decrease in the cholesterol levels are groupped and defined as λ and μ, respectively. Schell in his thesis has tried to find time for an individual increase from no blockage to a potentially dangerous point. The process was modelled as a path started at (0, 0) and ended at a critical level, Y=x. This process shows a fluctuation that touches critical levels and it is the same occurrence as a queueing system in which the number of customers increases and decreases. In Schell's (1994) paper, probabilistic methods, two-sided Ballot theorem, were applied and were compared to other papers' queueing models (9).

Another study on queueing theory and its real life application was carried out by Myasnikova et al (1996) (16). Myasnikova et al. (1996) has investigated the queueing system of repair mechanisms of the cells which were exposed to potentially lethal radiation by using three different models. In the first model, misrepair of radiation-induced lesions with respect to repair errors with a constant probability was examined. In the second one, the existence of a mechanism of spontenous lesion fixation was studied. The third one included the first and the second models together. Models of Myasnikova et al (1996) were based on pure death process with multiserver queueing system. The arrival rate (the number of lesions) is distributed as a Poisson distribution with parameter θD (where θ : the expected number of lesions per unit dose, D : the amount of dose) and the service times are exponentially distributed with parameter μ . In the paper of Myasnikova et al (1996), some cases such as repair and misrepair of DNA and cell death could occur when cells were exposed to potentially lethal radiation. Therefore, it was possible to apply different queue models in their research. However, in our research, we were interested in only insulin level and number of insulin receptors which allowed us to apply only one model of queueing model. In our study only one queue is formed; however, in the paper of Myasnikova et al (1996), more than one queue can be formed. Also when the two researches are compared, Myasnikova et al. (1996) examined the complete cell; however, we examined very small part of cell, just a small unit on the cell surface (16).

Arun (2002) has also examined the applicability of queueing theory on urinary system (6). In his paper, urine boluses, activity of pumping and micturition correspond to arrivals from kidney to bladder, bladder and bladder outlet, respectively. He also proposed that queueing theory could be a good model to describe the effects of alcohol on the lower urinary tract. In another study of Arun (2000), poisoning was thought as a queueing problem. The cases, arrials as intake of toxins and service as detoxification and elimination of the toxin, were considered. Departure process is the detoxified toxin or departing toxin from the body (5).

Number of insulin receptors are associated with some insulin based metabolic disorders (17,18). Therefore, finding optimal number of insulin receptors may be of importance to evaluate the patients' situations. In our study, we have obtained the optimal number of insulin receptors as $4x10^3$ receptors/red cells. This value is very close to the values described in Makris et al (2004) and Makris et al. (1998) (17,18).

In conclusion, the data reveals that queueing theory can be applied on insulin and its receptor numbers. Estimation that will be obtained from queueing theory may identify some problems in the ethiology of some metabolic disorders. Further studies strongly warrant the application of queueing theory on the other functions of human metabolism.

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