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An Improved Mathematical Model of Solute Kinetic During Hemodialysis

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Abstract. In this paper, we modify Cronin's model by defining the toxins generated by the organ mass compartment as the sum of the toxins used up by the extracellular compartment and the muscles mass adipose tissues compartment. The improved model clearly describes that the concentration of toxins for small patients remains low throughout the dialytic interval. The interdialytic phase starts with the inverted replica of the dialytic interval; a natural physiological phenomenon. However, the concentration of toxins remains high throughout the interdialytic interval which keeps the smaller patients comparatively at more mortality risks than the larger patients during the maintenance hemodialysis. This phenomenon is further verified by the time average concentration of the toxin in the extracellular compartment.

AMS (MOS) Subject Classification Codes: 92C45, 34A34
Key Words: Hemodialysis; Obesity Paradox; Concentration Gradient; Mathematical Modeling.

1. THE INTRODUCTION

Hemodialysis is alternative for the function which is to be done by the normal kidneys. It is needed when the Glomerular Filtration Rate (GFR) of the kidneys is less than 15mL/min. When the kidneys cease their functions, it keeps the body balanced, removes waste products and excess fluid on one hand and keeps the level of certain chemicals such as potassium, sodium and bicarbonate safe in the blood on the other hand. Obesity is not only a risk factor for other diseases, but also it is itself a disease. It increases the work of the heart, changes pulmonary, endocrine and immunological functions. It causes cardiovascular, diabetic, pulmonary obstructive, arthritis and cancer diseases [8]. There is also a close relation between obesity and Alzheimer's disease; see [10] and [9]. However, most of the studies on the association between obesity and the hemodialysis have shown that the physically smaller patients have higher mortality risks than the physically larger patients on the maintenance hemodialysis(MHD). This is called the obesity paradox.

The obesity paradox was first described in 1999 in overweight and obese people undergoing hemodialysis [17] and has since been found in those with heart failure [18], myocardial infarction [19] and acute coronary syndrome [13]. In general, a high body mass index(BMI) is associated with increased cardiovascular diseases but the effect being overweight with $BMI = 25$ to 30 or obesity with $BMI > 30$ in patients with the chronic kidney disease (CKD) undergoing MHD is paradoxically in the opposite direction i.e., a high BMI is associated with enhanced survival rate [6]. Obesity has been found to be associated with a survival advantage in hemodialysis patients [12].

Other factors may have a paradoxical relationship with patients on dialysis, however the finding is more consistent and persuasive for obesity [3], [14].

Most of the studies so far have found a direct relationship between the body mass and the survival on dialysis, while a few studies have not. In a study by Kaizu et al [5], on 116 hemodialysis patients from Japan spanned over 12 years in the early 1980, body mass of more than 23.0 showed lower survival rates compared to the patients with body mass of $17.0 - 18.9$. Since this study is followed up by the longest period and small sample size, it is, thus, possible that obese patients may have better survival in the short term, but not necessarily in the long term [15].

High BMI appears protective in hemodialysis patients, but the question still remains, which part of the body composition, fat or lean body mass, are basically related with the survival [11].

The exact reasons for this irregularity during the hemodialysis have not been yet known. However, the experts give two manifestations for this irregularity [2]:

(1) The rate of generation of the uremic toxins by the higher metabolic rate compartments(HMRCs) i.e., visceral organs is higher in smaller patients in proportion to that in the larger patients. So the concentration of toxins in larger patients due to larger body sizes is less than the concentration of the toxins in the smaller patients. As a result, the smaller patients proportionally produce more uremic toxins than the larger patients.
(2) In the larger patients, muscle mass and the adipose tissues hold the uremic toxins from the extracellular tissues and so reduce their concentration in the extracellular fluid as compared to the smaller patients.

In order to check the truthfulness of the above manifestations, some mathematical models explaining solute kinetic in the body during the hemodialysis have been proposed by different researchers. These may be classified into one-pooled, two-pooled, three-pooled and higher pooled urea-kinetic models. For a detailed study of the one-pooled and two-pooled urea-kinetic models, one can see [1]. The first three-pooled mathematical model was given by Cronin et al [2]. The model is important as all the subsequent higher-pooled models are based on it. For example, [7] is one of them. However, Cronin's model has a serious flaw which we intend to remove in this paper. Before we remove this, it is beneficent to summarize the principle of the working of the hemodialysis.

Hemodialysis works on the theory of the diffusion of solutes and ultra-filtration of fluid across a semi-permeable membrane. For a study of diffusion of toxin across the cell membrane, one can see [4]. Blood flows by one side, and dialysis solution on the opposite side of the membrane. Smaller solutes and fluid pass through the membrane. The blood flows in one direction and the solution flows in the opposite. The counter-current flow of the blood and solution maximizes the concentration gradient of the solutes between the blood and solution, which helps to remove more urea and toxins from the blood. The concentrations of the solutes are comparatively high in the blood, but low in the dialysis solution and constant replacement of the solution ensures that the concentration of undesired solutes is kept low in the solution.

1.1. **Cronin's Model.** Cronin's model consists of a system of three ordinary differential equations (ODEs) describing the concentrations of toxins in three compartments; the organ mass compartment(**OM**), the muscle mass and adipose tissue compartment(**MMAT**) and the extracellular fluid compartment(**E**). The volumes of three compartments are respectively V_{OM}, V_{MMAT} and V_E and the concentrations of toxins in the three compartments are given by C_{OM}, C_{MMAT} and C_E respectively. Flow is shown in the Figure 1. The system of differential equations describing the rates of concentration of toxin in terms of its mass in all the three compartments is given by

$$\begin{aligned} V_{OM}\frac{d(C_{OM})}{dt} &= G - K_{OM}(C_{OM} - C_E), \\ V_{MMAT}\frac{d(C_{MMAT})}{dt} &= K_{MMAT}(C_E - C_{MMAT}), \\ V_E\frac{d(C_E)}{dt} &= K_{OM}(C_{OM} - C_E) - K_{MMAT}(C_E - C_{MMAT}) - K_d C_E. \end{aligned} \tag{1. 1}$$

The first equation describes the generation of toxins by the high metabolic rate compartment and its release into extracellular fluid. The second shows the release of toxins being stored in muscle and adipose tissues to the extracellular fluid. The third shows the changing concentration of the toxins in the extracellular fluid as it comes in from the two sources and leaves via the dialysis taking place.

In Cronin's model [2], the middle molecule generation rate G without being defined has been used as

$$G = V_E(C_E - C_{E_0}) + V_{MMAT}(C_{MMAT} - C_{MMAT_0}) \tag{1. 2}$$

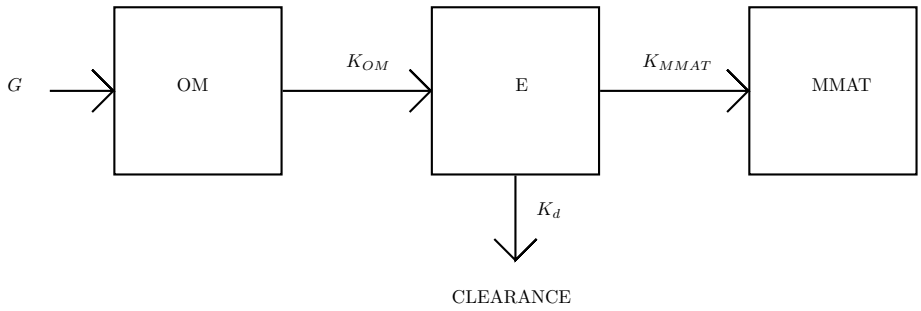

FIGURE 1. Structure of a Three-Pooled Solute Kinetic Model.

This equation is unit-inconsistent and makes no meaning as the unit of G is g/day whereas the expression on its right-side clearly does not possess the same unit. The use of this expression for G in the model makes it wrong and the results produced therein unauthentic and unreliable. Therefore it is imperative to remove this discrepancy by correctly defining the middle molecule generation rate G. For this purpose, we proceed in a manner described in the next section.

2. IMPROVED MODEL

We have observed that G as given in Eq.(1. 2) above as in Ref. [2] is incorrect. Now as long as the toxins are generated by the **OM** compartment, it is used up simultaneously by the other two compartments **E** and **MMAT**, therefore the rate of generation of the toxins by the **OM** compartment is equal to the sum of the rates at which they are used up by the **E** and **MMAT** compartments. This gives rise to the following equation:

$$K_{OM}(C_{OM} - C_E) = K_{OM}(C_E - C_{E_0}) + K_{MMAT}(C_{MMAT} - C_{MMAT_0}) \quad (2.\ 3)$$

So our improved model consists of the three ordinary differential equations given by Eqs.(1. 1) along with the Eq.(2. 3).

2.1. **Steady States Solution.**

Steady state solution of the model is

$$(C_{OM}, C_{MMAT}, C_E) = \left(G\frac{K_{OM} + K_d}{K_{OM}K_d}, \frac{G}{K_d}, \frac{G}{K_d} \right).$$

This solution describes that the steady state of the system can not be obtained during the dialysis phase. Moreover, system has the same steady states for the **MMAT** and the **E** compartment viz., $\frac{G}{K_d}$.

2.2. **Analytic Solution.**

We are interested in evaluating the extracellular concentration C_E during the dialytic and inter-dialytic intervals. Simultaneous numerical solution of the System (1. 1) not meet our purpose. However, in order to get a better understanding of the solute kinetic explained by the system in the extracellular compartment, we keep the **OM** compartment in steady state. This gives $\frac{d(C_{OM})}{dt} = 0$, and so from first equation of the

System (1. 1), we get $K_{OM}(C_{OM} - C_E) = G$. Therefore, the system of the differential equations for dialytic interval after taking the **OM** compartment at steady state becomes:

$$\begin{aligned} V_{MMAT}\frac{d(C_{MMAT})}{dt} &= K_{MMAT}(C_E - C_{MMAT}), \\ V_E\frac{d(C_E)}{dt} &= G - K_{MMAT}(C_E - C_{MMAT}) - K_dC_E. \end{aligned} \tag{2. 4}$$

For the interdialytic interval, we take $k_d = 0$ and $K_{OM}(C_{OM} - C_E) = G$ as from the steady state of the **OM** compartment, so the system of differential equations for the interdialytic interval becomes:

$$\begin{aligned} V_{MMAT}\frac{d(C_{MMAT})}{dt} &= K_{MMAT}(C_E - C_{MMAT}), \\ V_E\frac{d(C_E)}{dt} &= G - K_{MMAT}(C_E - C_{MMAT}). \end{aligned} \tag{2. 5}$$

We separately solve the improved model for the dialytic and interdialytic intervals analytically.

2.2.1. *Analytic Solution for the Dialytic Phase.* For the **dialytic interval**, we solve the system of Eqs. (2. 4) simultaneously. We take value of C_E from second equation interms of other terms and place it in first equation. The system converts into a second order linear differential equation with constant coefficients with the initial conditions that $C_E(0) = C_{MMAT}(0) = \frac{G}{K_d}$ in the consequence of the steady-state of the system. The analytic solution by the use of the characteristics equation method is given by:

$$C_E = c_1e^{m_1t} + c_2e^{m_2t} + \frac{G}{K_d} \tag{2. 6}$$

where

$$m_1 = -\frac{1}{2V_EV_{MMAT}}(V_{MMAT}K_d + V_EK_{MMAT} + K_{MMAT}V_{MMAT} + \sqrt{(V_{MMAT}K_d + V_EK_{MMAT} + K_{MMAT}V_{MMAT})^2 - 4K_{MMAT}V_{MMAT}K_dV_E})$$

$$m_2 = -\frac{1}{2V_EV_{MMAT}}(V_{MMAT}K_d + V_EK_{MMAT} + K_{MMAT}V_{MMAT} - \sqrt{(V_{MMAT}K_d + V_EK_{MMAT} + K_{MMAT}V_{MMAT})^2 - 4K_{MMAT}V_{MMAT}K_dV_E})$$

and

$$c_2 = \frac{G(K_d + m_1V_E) - K_d(V_Em_1 + K_d)x_0}{K_dV_E(m_2 - m_1)}$$

$$c_1 = C_{E_0} - \frac{G}{K_d} - c_2,$$

2.2.2. *Analytic Solution for the Interdialytic Phase.* The model for interdialytic interval is given by the set of equations(2. 5). The solution of this system involves the computation of the values of $C_{MMAT}(t)$ during the dialytic interval and again at the beginning of the interdialytic interval to be used as the initial condition in the system. In order to get a workable solution, we need the initial value of the concentration C_{MMAT} at the beginning of the interdialytic interval which is off-course the value of the C_{MMAT} at the end of the dialytic interval. This creates an additional problem in computing $C_{MMAT}(t)$. In order to avoid this extra work, we need an equation which gives a workable solution for our purpose. Cronin-Finn [2] et. al., used Eq. (1. 2), which makes the model wrong as we have already explained. Here we use the following equation:

$$G = K_{OM}(C_E - C_{E_0}) + K_{MMAT}(C_{MMAT} - C_{MMAT_0}) \tag{2. 7}$$

which is obtained by putting $K_{OM}(C_{OM} - C_E) = G$ in Eq.(2. 3). This equation defines the middle molecule generation rate G as the total of the middle molecules sequestered by the **OM** and the **MMAT** compartments . Thus we are led to the following equations using the steady state of the **OM** compartment i.e., $K_{OM}(C_{OM} - C_E) = G$:

$$\begin{aligned} V_E\frac{d(C_E)}{dt} &= G - K_{MMAT}(C_E - C_{MMAT}),\\ G &= K_{OM}(C_E - C_{E_0}) + K_{MMAT}(C_{MMAT} - C_{MMAT_0}). \end{aligned} \tag{2. 8}$$

Taking the value of C_{MMAT} from the second equation and putting in the first equation, we get the following differential equation for the concentration of the toxins in the extracellular compartment:

$$V_E\frac{d(C_E)}{dt} + \left(\frac{K_{MMAT} + K_{OM}}{V_E}\right)C_E = \frac{2G}{V_E} + \frac{K_{OM}C_{E_0}}{V_E} + \frac{K_{MMAT}C_{MMAT_0}}{V_E} \tag{2. 9}$$

This is first order linear differential equation. The solution of this equation is obtained by making it exact by the use of integrating factor and is given by

$$C_E = \frac{2G + K_{OM}C_{E_0} + K_{OM}K_{MMAT_0}}{K_{OM} + K_{MMAT}} + re^{-\frac{1}{V_E}(K_{MMAT}+K_{OM})t} \tag{2. 10}$$

where r is constant of integration. To find r numerically, we take $C_E(0)$ as the concentration of the toxins of the extracellular compartment **E** at the end of the dialytic interval.

3. SIMULATIONS

In lieu of the manifestations of the obesity paradox given in Section 1, we consider three patients with different masses classified as *small patient*, *medium patient* and *large patient* with the values of their parameters given in the Table 1. This is in relation to test the first manifestation. We take the dialysis clearance rate, $K_d = 200$ ml/min. Now as K_{MMAT} denotes the rate of the release of the toxin by the muscle mass adipose tissues compartment(**MMAT**) into the extracellular compartment, so we take different values of the muscle mass adipose tissues transfer rate as $K_{MMAT} = 50$ mL/min, $K_{MMAT} = 5$ mL/min, $K_{MMAT} = 1$ mL/min, 0.1 mL/min, 0.01 mL/min and 0.001 mL/min, and see its effects on the extracellular concentration C_E of toxin on the three patients in the extracellular compartment. This is in relation to the second manifestation of the obesity paradox.

TABLE 1. Patients' parameters

Parameters	Small Patient	Medium Patient	Large Patient
BW	40 kg	70 kg	100 kg
V_E	23200 mL	40600 mL	58000 mL
V_{OM}	11280 mL	17220 mL	21000 mL
V_{MMAT}	1520 mL	5180 mL	11000 mL
G	30.5556 mg/min	48.2639 mg/min	59.7222 mg/min
C_{MMAT_0}	1000 mg/L	1000 mg/L	1000 mg/L
C_{E_0}	1000 mg/L	1000 mg/L	1000 mg/L

There are different methods to calculate the value of G; one can see [20] and [16]. However, we follow [2] to take $G \approx BW(1.4 - 0.005BW) - 4$.

For dialytic interval, we take time $t = 4$ hours and the initial concentrations of toxins for the extracellular and the **MMAT** compartments each as 1000 mg/L. For the inter-dialytic interval, time $t = 2.3$ days, the initial concentration for toxins for the extracellular compartment is the extracellular concentration of the toxins at the end of the dialytic interval. For the modified model, we take $K_{OM} = 45$ mL/min. We simulate the analytic solutions of the modified model for values of the parameters given in the Table 1.

We first plot Eq. (2. 6) for the dialytic interval with initial conditions taken from the steady state of the **OM** compartment for the three patients and then we plot Eq. (2. 10) for the interdialytic interval with the initial conditions taken from the values of the extracellular concentrations for the three patients where the dialytic interval finishes.

The interdialytic interval is taken of duration 3312 minutes $(2.3$ days$)$.

Our simulations are simply classified into three categories viz., dialytic interval and interdialytic interval and the time average concentration (TAC) of toxins for extracellular compartment for the three categories of patients. Simulation results are given in Figures[2, 3, 4, 5] and Tables [3, 2].

3.1. **Dialytic Interval.** For dialytic interval, we simulate the Solution(2. 6) for selected values of K_{MMAT} for three patients. The results are shown in the Figure 2.

3.2. **Inter-dialytic Interval.** For inter-dialytic interval, we simulate solution(2. 10) for selected values of K_{MMAT} for three patients. The simulation results are shown in Figure 3.

4. RESULTS

(1) For dialytic interval, the simulations for different values of K_{MMAT} show almost the same results signifying the fact that the small patient has lower final concentration than the medium and the large patients. By increasing the **MMAT**-Mass transfer coefficient K_{MMAT}, the concentration of toxins in the smaller patient reaches its steady state faster as compared to its lower value.

(2) For inter-dialytic interval, we observe the behavior of the extracellular concentration of the intermediate molecular weight species (IMWS) soon after dialytic interval for the same above four different values of the transfer coefficient (K_{MMAT})

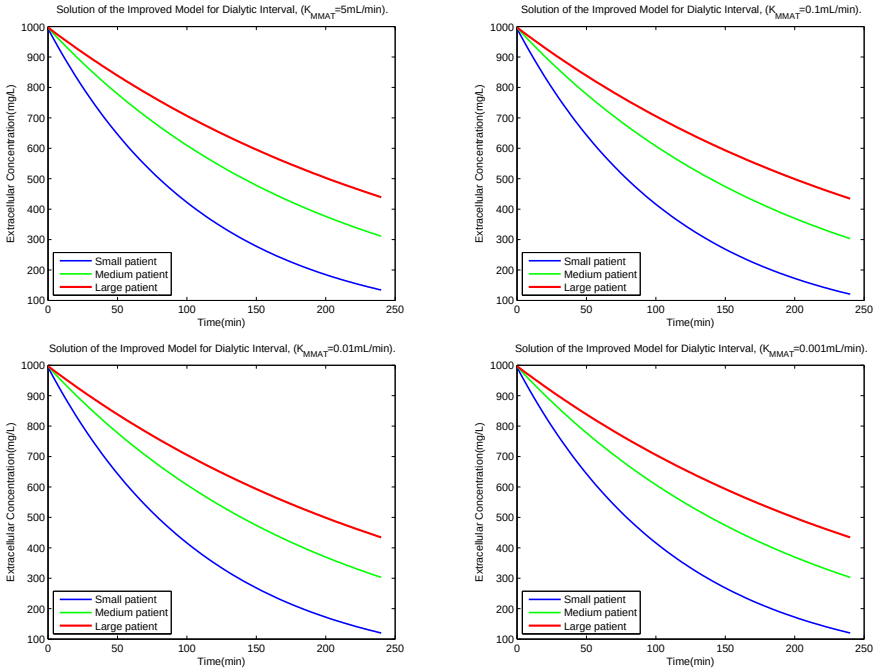

FIGURE 2. Solution for the Improved Model for Selected Values of the Transfer Coefficient K_{MMAT} for Three Patients-Dialytic Interval.

up to 3312 minutes for the three patients viz., *small patient*, *medium patient* and *large patient*.

During the initial phase of the inter-dialytic interval up to 200 minutes soon after the dialytic interval, the concentration of the toxin for all the four values of the **MMAT**-Mass transfer coefficient (K_{MMAT}) represents more or less the same pictures. The concentration of toxin in the small patient remains lower than the medium and large patients, but it increases with a higher rate. It crosses the concentrations of the medium and large patients around 200 minutes. In this case, the high value of the K_{MMAT} enhances the concentration of toxin as is evident in the first figure of the panel.

The behavior of the representative concentrations up to 1000 minutes, for the smaller, medium and the large patients is almost identical. Beyond 200 minutes to the end of this phase, the concentrations for the smaller patients remains high for all values of the **MMAT**-Mass transfer coefficient than the medium and large patients. Beyond 1000 minutes to 2000 minutes , the concentration of the toxin in the extracellular compartment of the small patient remains high than the other patients. The concentration in the small patient attains its steady state at 2000 minutes whereas those of the medium and large patients do not for $K_{MMAT} = 5$ mL/min.

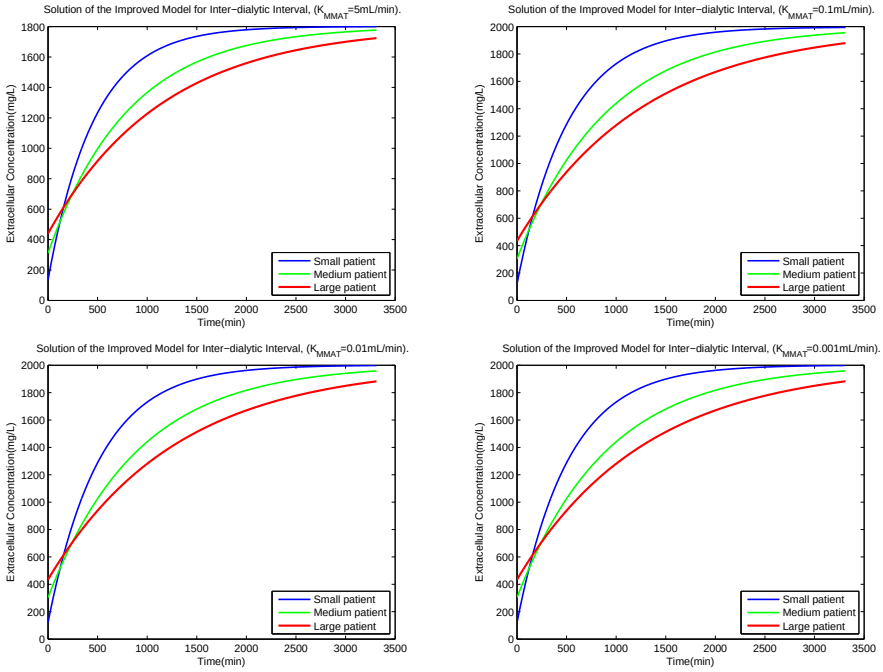

FIGURE 3. Solution of the Improved Model for Selected Values of the Transfer Coefficient K_{MMAT} for Three Patients-Interdialytic Interval.

After 2000 minutes when the concentration of the small patient has almost achieved its almost steady states for $K_{MMAT} = 5$ mL/min, the lowering values of the K_{MMAT} delays it to get its steady state; it takes the steady states before 3312 minutes whereas the concentrations of the toxin in the medium and the large patients do not attain their steady states within 3312 minutes as is evident in Figure 3.

Thus by increasing the value of **MMAT**-Mass transfer coefficient K_{MMAT}, we observe that the concentration of the IMWS solute for smaller patient reaches the almost steady states more rapidly as compared to medium and large patients. The time required for reaching the steady states in smaller patients is much less than that required by the medium and large patients.

(3) In order to magnify the difference between the solute kinetic in all the three patients in relation to the K_{MMAT} during the dialytic and interdialytic phases, we take $K_{MMAT} = 50$ mL/min. The result is shown in the Figure 4. The figure shows that the effect of K_{MMAT} is not so enormous during the dialytic period, but it is more prominent during the interdialytic phase signifying the better survival chances for the large patient.

(4) The time average concentrations (TAC) signifies the average values of the C_E spanned separately over the whole dialytic and interdialytic intervals. For dialytic interval, its value for the small patients remains low than the other two patients,

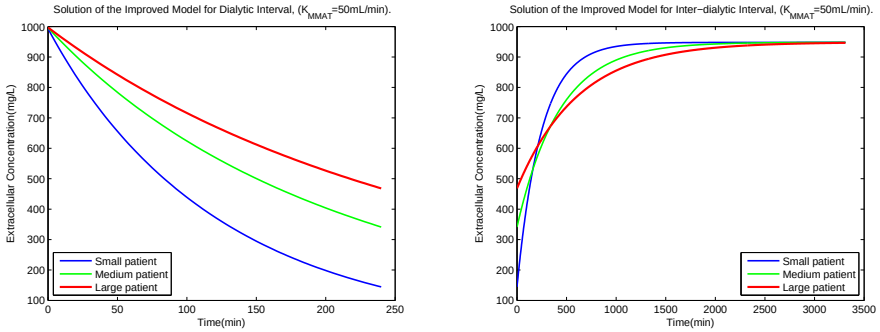

FIGURE 4. Comparison of the Solute Kinetic During Dialytic and Interdialytic Intervals.

TABLE 2. Time Average Concentration for Three Patients for Dialytic Interval

K_{MMAT}	Small Patient	Medium Patient	Large Patient
50	437.3208	603.2818	692.4170
5	424.8925	586.9132	679.6163
1	419.2186	584.1350	678.0152
0.1	417.5902	583.4626	677.6418
0.01	417.4189	583.3943	677.6042
0.001	417.4017	583.3875	677.6004

TABLE 3. Time Average Concentration for Three Patients for Interdialytic Interval.

K_{MMAT}	Small Patient	Medium Patient	Large Patient
50	888.4	869.8	860.3
5	1567.3	1442.2	1352.2
1	1678.3	1527.8	1420.7
0.1	1705.3	1548.3	1436.9
0.01	1708.0	1550.4	1438.6
0.001	1708.3	1550.6	1438.7

however it increases as long as K_{MMAT} decreases as is evident from its values in Table 2. For interdialytic intervals, its value for the small patients remains high for all values of the K_{MMAT} as compared to the other two patients as are clear in Table 3 and Figure 5. This keeps the small patient again at risk as compared to the medium and large patients. The time average concentration for each value of K_{MMAT} for the small patient remains higher than that of the medium and large patient in interdialytic interval. Alternatively, we can say that the survival risk of the small patient is independent of the muscles mass adipose tissue transfer rate K_{MMAT}.

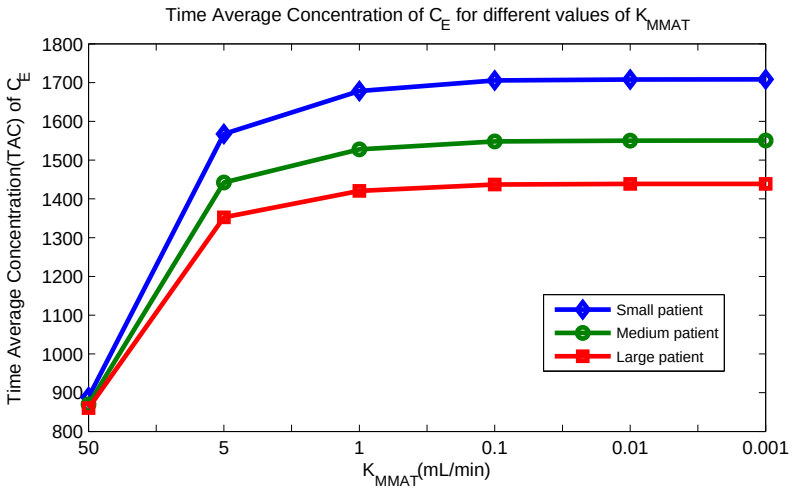

FIGURE 5. Time Average Concentration of Extracellular Compartment for Interdialytic Interval

5. CONCLUSION

Maintenance hemodialysis spreads over several phases of dialytic and interdialytic treatments of the patient. The improved model describes the kinetic of toxins in three patients during the dialytic and interdialytic phases in accordance with the prevalent literature.

The simulations of the model during the dialytic interval show that the concentration of toxins in small patient remains low through the phase, however, even the high value of the K_{MMAT} in this phase brings no prominent affects on the concentration of toxins in three different patients i.e., these results are independent of the K_{MMAT} mass transfer rate as are clearly shown in Figure 4.

The results of the model for the interdialytic phase are more important. Simulations show that the interdialytic phase begins with the shadow or the inverted replica of the dialytic phase during almost first 200 minutes with the concentration of toxins in the small patient increasing rapidly lagging behind those of the medium and large patient as shown in Figure 3. Simulations beyond that show high concentration of toxins in small patients as compared to medium and large patients throughout the interval. The steady state for toxins in small patient is achieved much earlier than that of other patients which is more evident with enhanced value of K_{MMAT}. Small patient, even for low values of K_{MMAT}, exhibits a higher extracellular fluid concentration of toxins than the larger patients as is evident in Figure 3.

The time average concentration (TAC) of extracellular concentration for almost all values of K_{MMAT} for the small patient remains higher than that of the medium and large patient as is shown in Figure 5.

6. ACKNOWLEDGEMENTS

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