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Solute Kinetic Model in Haemodialysis Process: A Review and its Relevance to Sustainable Development Goals (SDGs)

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Abstract

Haemodialysis process is essential for patients with end-stage renal disease (ESRD), serving as a life-saving treatment that substitutes the kidneys' function in removing uremic toxins and maintain fluid balance in the bloodstream. Solute kinetic models provide quantitative framework to predict solute clearance, assess treatment parameters, and improve patient outcomes. This review offers insight into approaches in solute kinetic modelling in improving haemodialysis process and its alignment with Sustainable Development Goals (SDGs). The review highlights the essential variables that influence solute kinetic models towards achieving quality efficacy in dialysis treatment. These variables include dialyzer clearance, residual renal clearance, rate, and location of generation of the substance in question, compartment volumes, intercompartment transfer and distribution coefficient. Solutes (dissolved substances in the blood that need to be removed or regulated) were classified and approaches to the solutes kinetic modelling were explained. Solute kinetic models contribute to achieve SDG Goals, SDG 3 (Good Health and Well-being); SDG 9 (Industry, Innovation, and Infrastructure); SDG 10 (Reduced Inequalities), and SDG 12 (Responsible Consumption and Production), through improved dialysis. These can be achieved by ensuring effective renal replacement therapy, reducing mortality associated with kidney disease, promoting equitable accessible dialysis treatment, and minimizing environmental waste in dialysis procedures.

Keywords: Kinetic Models; Haemodialysis; Renal Replacement; Kidney Disease; SDGs

Abbreviations

ESRD: End Stage Renal Disease; SDGs: Sustainable Development Goals; UKM: Urea Kinetic Modeling; BMI: Body Mass Index; DOQI: Dialysis Outcomes Quality Initiative; SKM: Solute Kinetic Modelling

Introduction

Haemodialysis is a renal replacement therapy for the removal of accumulated toxic waste and fluids in patients with end-stage renal disease (ESRD). The adequacy and effectiveness of haemodialysis are important to patient outcomes, affecting not only the removal of toxins but also the overall quality of life [1]. Mathematical modelling of haemodialysis process is an essential tool in understanding, predicting, and optimizing treatment outcome. Researchers have used mathematical models to simulate the dynamic processes occurring during dialysis, predict outcomes under various conditions, and refine treatment protocols to meet individual patient needs. These models help unravel the intricacies of solute transport, membrane interactions, and

fluid dynamics within the dialyzer, providing a foundation for advancing both the theoretical and practical aspects of haemodialysis. Dialysis is a rate governed membrane separation process whereby micro solute present in a feed solution is driven across a semi-permeable membrane using concentration gradient at a greater rate than macro solute to the receiving solution (dialysate) thereby restraining the macro solutes present in the feed solution from passing to the dialysate stream [2,3]. Solute kinetic models describe the transport and removal of solutes (waste products) during haemodialysis. This review aims to provide different approaches for solute kinetic modelling in haemodialysis process. It explores the classification of solutes, principles of solute kinetic models, their applications in clinical and research settings, and the key factors that influence their performance. In addition, the review explores the intersection of solute kinetic model in haemodialysis process with the SDGs.

Solute Kinetic Models

The process model is a representation of the important aspect of a system in mathematical form to describe the behaviour of a system [4,5]. It can also be described as the tool to analyze the system response at differing input conditions and to describe the behavior of a physical or chemical process [6,7]. They are also applied in biological fields to obtain parameters that cannot and/or easily be obtained in other ways [8].

A kinetic model is used to describe the changes in a physical entity (such as concentration, mass, energy) between a system and the environment over time when applied to hemodialysis [9]. Kinetic models incorporate fluid mechanics and mass transport mechanisms to represent the whole patient–hemodialyzer system [10]. Kinetic models help the physician to predict the changes in the body compartments that are not accessible because of complexity involved in the exchange between the body fluids (plasma, interstitial and intracellular) and dialysis fluid for water, toxins and electrolytes [10-12]. Solute kinetic modeling helps in evaluating dialysis efficiency. Solute kinetic models describe the transport and removal of solutes (waste products) during hemodialysis.

Solute kinetic models consist of a set of ordinary differential equations describing changes in solute mass, concentration and distribution volume in body compartments and the dialyzer. These models can be used to predict the concentration of solutes in the blood over time and to assess the efficiency of dialysis treatments. These variables include dialyzer clearance, residual renal clearance, rate and location of generation of the substance in question, compartment volumes, intercompartment transfer and distribution coefficient [11,13].

Dialyzer Clearance: Dialyzer clearance is used to determine the rate of removal of a solute from blood per unit time. It depends not only on the treatment method but also on the dialyzer characteristics. Dialyzer clearance for a particular solute (urea, creatinine, phosphate, vitamin B12, etc.) is characterized by its diffusive clearance values [10]. Dialyzer clearance is calculated from the mass balance equation [13]:

$$KC_{Bi} = Q_{Bi}C_{Bi} - Q_{Bo}C_{Bo} \quad (1)$$

K= clearance (mL/min), Q_{Bi}= blood flow at the dialyzer inlet, Q_B0= blood flow at dialyzer outlet, C_Bo and C_Bi = concentration of the solute (mmol/L) for output and input respectively

If Q_F is ultrafiltration rate and blood flow is Q_B, then

$$Q_{B0} = Q_{Bi} - Q_F \quad (2)$$

Substituting Equation (1) in Equation (2) and substituting $Q_B=Q_{Bi}$, $Q_F=0$ gives general clearance for haemodialysis as [11]:

$$K=K_{HD}=Q_B\frac{C_{Bi}-C_{B0}}{C_{Bi}}=Q_B\left(1-\frac{C_{B0}}{C_{Bi}}\right) \quad (3)$$

However, if ultrafiltration is present, that is, $Q_F\neq0$, the general clearance is written as,

$$K=\frac{Q_{Bi}C_{Bi}-\left(Q_{Bi}-Q_F\right)C_{B0}}{C_{Bi}}=K_{HD}+Q_F\frac{C_{B0}}{C_{Bi}} \quad (4)$$

where K_{HD}= solute clearance by diffusion (no ultrafiltration), $Q_F\,C_{B0}/C_{Bi}$ = convective part of the solute transport.

Residual Renal Clearance: Residual renal clearance is used to determine the error that might occur during the estimation of the concentration of substances in a dialysis patient. These errors might occur due to difficulty in passing small volumes of urine or a change in plasma creatinine concentration between dialysis treatments. Hence, urine is usually collected for 24 h. and analyzed for urea and creatinine to determine the residual renal function [11,13]. For a particular substance, Equation 5 is used to calculate the residual renal clearance (Kr) [11].

$$K_r=\frac{\text{excretion rate}}{C_e}=\frac{C_{urine}V_{urine}}{T_{urine}}\frac{1}{C_e}=\frac{\Delta M_r}{T_{urine}}\frac{1}{C_e} \quad (5)$$

Where C_e = plasma solute concentration, C_{urine} = solute concentration of urine, V_{urine} = volume of urine, T_{urine} = Time

of urine collection and ΔM_r = mass of solute removed from the kidney.

Generation Rate: Synthesis of toxic substances takes place either in the intracellular or extracellular compartments [13]. At a steady state and with continuous dialytic treatment, the solute generation rate (G) is balanced by solute removal rate (Kss) with a constant concentration within the patient body [11]. Assume a single pool model, G is given by:

$$G=V\times\frac{C_b(t)-C_b(0)}{t}+K_R\times\dot{\bar{C}}_b \quad (6)$$

where $\bar{C}_b$ = mean value of $C_b(t)$ from time t=0 to t=t., V = distribution volume (mL), Cb (0) and Cb(t) = plasma concentration at the beginning and end of the measurement period (t), Kr = residual renal clearance.

Compartment Effects: There are large numbers of physical compartments present in the human body where most of the toxins to be removed reside aside from the blood [11,14,15] . A compartment can be referred to as a space that is separated from the environment and allows the controlled exchange of energy, mass and information with the environment [16]. In developing a model in haemodialysis, analysis of physiological and chemical interaction between the body fluid compartments is important. The compartments can be one single pool or set of interconnected pools (two or more compartments) with each of them being characterized by homogeneous internal solute concentration (C_1, C_2 ...) and distribution volume (V_1,V_2,) all changing with time due to changes in their transport process.

A human body can be described mathematically by considering it as a single pool (one compartment) or a set of interconnected pools (two or multiple compartments). One compartment assumes that the body is a single, well-mixed space with high permeability of cells to the modeled solute and a rapid flow of blood that transports solute through a perfused body. For two-compartment models, the patient body is divided into intracellular and extracellular compartments. Moreover, multiple compartment models can predict changes in body compartments that are inaccessible to the clinician but may be relevant to clinical side effects.

The transport processes can be modelled by considering input and output amount of solute, solute generation (G) and metabolic elimination. Each compartment is expressed mathematically as an ordinary differential equation to simulate changes in concentrations of solutes of dialysis patients and describe changes of solute concentration, mass and distribution volume in body compartments and the dialyzer. The schematic diagram for the one and two-compartment models is shown in Figure 1 [11,13,17].

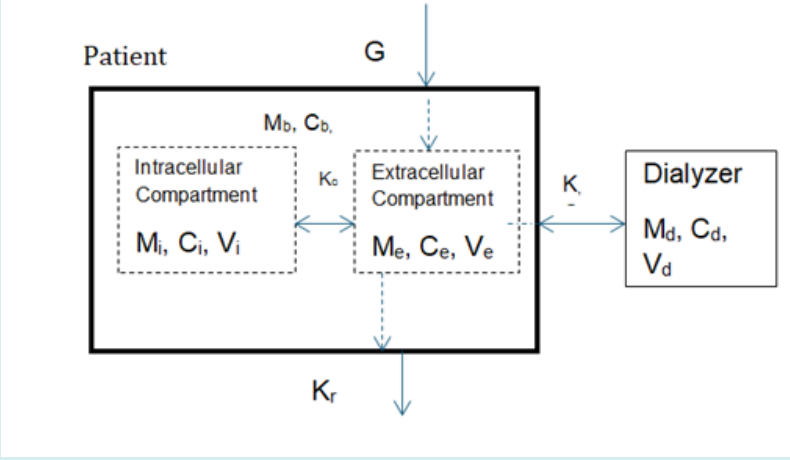

Figure 1: One and Two Compartment Models for Solute Distribution Volume [11].

For one compartment solute distribution, the rate of change of solute mass in the body (Mb) is given by:

$$\frac{dM_b}{dt}=\frac{d(C_bV_b)}{d} \quad (6)$$

The rate of change of solute mass in the dialysate (Md) is:

$$\frac{dM_d}{dt}=d(C_dV_d)/dt \quad (7)$$

where C_b and C_d = concentration of solute in the body and dialysate and V_b and V_d = fluid volume in the body and dialysate.

The mathematical description of mass balance of total solute

mass is given by Debowska M, et al. [11]:

$$\frac{d(C_b V_b)}{dt} = G - K(C_b - C_d) - K_r C_b \quad (8)$$

$$\frac{d(C_d V_d)}{dt} = K(C_b - C_d) \quad (9)$$

where K= solute clearance, K_r=residual renal clearance, G= rate of solute generation

However, for more than one compartment model, each compartment will be represented by a set of the differential equations which have to be solved simultaneously using any appropriate numerical integration methods [17]. In this case output of one compartment will serve as input to next compartment which is serial arrangement.

An example is the two-compartment model where solute removal by the hemodialyzer is a function of the solute concentration in the extracellular compartment Ce and is indirectly dependent on the intercompartmental mass transport coefficient Kc. It can be mathematically expressed as:

$$\frac{d(V_e C_e)}{dt} = K_c(C_i - C_e) - K(C_e - C_d) + G - K_r C_e \quad (10)$$

$$\frac{d(V_i C_i)}{dt} = -K_c(C_i - C_e) \quad (11)$$

$$\frac{d(V_d C_d)}{dt} = K(C_e - C_d) \quad (12)$$

where C_i and C_e = solute concentration in intracellular and extracellular compartments, V_i and V_d = fluid volume in the intracellular and extracellular compartment.

A review of the past work showed that hemodialyzer clearance and dialysis kinetic was first described by Wolf, et al. [18]. Also, Renkin, pioneered the mathematical description of dialysis. Bell, et al. applied to model to renal replacement therapy where a simulation was developed based on patient-hemodialyzer interaction while Sargent and Gotch introduced the one-compartment model to clinical practice for patient care. The solutes can be categorized based on their molecular weight range into small molecules, middle molecules and larger molecular as shown in Table 1 as defined by the European Toxin Work Group (EUTox) [19,20].

Classification of Solutes	Example (Molecular Weight)	Origin	Molecular Weight Range
Small molecules	Urea (60 Da)	Breakdown of proteins and amino acids.	<500
	Creatinine (113 Da)	Waste product from muscle metabolism.	
	Electrolytes (Na+, K+,... etc.) (134 Da)	Dietary intake and metabolic processes	
	Bicarbonates	A buffer that neutralizes acids in the blood.	
Middle molecules	Vitamin B12 (1355 Da)	Deficiencies in various vitamins and minerals.	500 – 15000
	Vancomycin (1448, Da)	Pharmacokinetics and clinical effectiveness.	
	Inuline (5200, Da) Endotoxin fragments (1000-15000 Da)	Dietary conditions	
	β2-microglobulin (11818 Da)	Protein associated with the immune system	
Large molecules	Myoglobin (17000)		>15000
	EPO (34000)		
	Proteins: e.g. Albumin (66000 Da)		

Table 1: Categorization of Solutes.

Urea Kinetic Modelling

Urea kinetic modeling (UKM) is the most widely used application of solute kinetic models in hemodialysis. Urea is used as a marker because it is a small, easily measurable solute and represents overall waste removal efficiency. The first solute kinetic modelling approach is Urea Kinetic Modelling (UKM) which was first investigated by Gotch in the mid – 1970 [10]. UKM is a method used for describing the combined effects of urea removal and generation taking

the total urea distribution within the body into consideration [14,21]. This was investigated for evaluation of dialysis adequacy, urea distribution volume equated to the total body water and protein catabolism rate [10,14], urea clearance to measure haemodialysis adequacy because urea clearance correlates more with clearances of all toxins [14,22]. Gotch and Sargent (1985), use the parameter known as Kt/V index or dialysis dose to describe the effectiveness of haemodialysis treatment. This dialysis index (Kt/V) is the urea clearance (K, ml/min) multiplying the length of dialysis treatment (t/min) and dividing the patients' volume of urea distribution (V, l). Several researchers [14,17,23,24] have worked on the standard to measure adequate dialysis dose using the one- or two-compartment model. However, a consensus was later reached that the Dialysis Outcomes Quality Initiative (DOQI) should be followed for its adequate measurement.

Indices For UKM Measurement

Standard Kt/V: This is a dialysis parameter usually used to determine the dose of dialysis therapy. It is the ratio of the dialyzer clearance (K), dialysis time (*t*), and the volume of distribution of urea (*V*). Researchers have developed various Kt/V models to estimate dialysis dose by utilizing pre and post dialysis blood urea nitrogen. These models are shown in Table 2, however, literature have supported the minimum haemodialysis dose of at least kt/V=1.2, optimal dose is yet to be given [22].

Model	UKM Formular
Lowrie Model	$\frac{Kt}{V}=\ln\left(\frac{C_o}{C_t}\right)$
Jindal Model	$\frac{Kt}{V}=0.04\left((C_o-C_t)/C_o\times100\right)-1.2$
Keshaviah model	$\frac{Kt}{V}=1.162\ln\frac{C_o}{C_t}$
Barth Model	$\frac{Kt}{V}=0.031\left((C_o-C_t)/C_o\times100\right)-0.66$
Calzavara Model	$\frac{Kt}{V}=(C_o-C_t)/(C_o+C_t)/2$
Daugirdas 1	$\frac{Kt}{V}=-\ln\left(\frac{C_t}{C_o}\right)-0.008\times t-\frac{UF}{Wt}$
Basile Model	$\frac{Kt}{V}=0.023\left((C_o-C_t)/C_o\times100\right)-0.284$
Ijely Model	$\frac{Kt}{V}=0.018\left((C_o-C_t)/C_o\times100\right)$
Daugidas 2	$\frac{Kt}{V}=-\ln\left(\frac{C_t}{C_o}-0.008\times t\right)+\left(4-3.5\times\frac{C_t}{C_o}\right)\times\frac{UF}{Wt}$
Kerr Model	$\frac{Kt}{V}=0.042\left((C_o-C_t)/C_o\times100\right)-1.48$
Azar Model	$\frac{Kt}{V}=-0.081+1.082\ln\left(C_o\right)-1.053\ln\left(C_t\right)$

Table 2: Different models for estimation of the Kt/V.

Urea Reduction Ratio (URR)

This is the percentage reduction in blood urea concentration during dialysis. Dialysis is adequate when URR is 65% and above [25,26]. URR can be determined using:

$$URR=100(1-(C_t /C_o)) \quad (13)$$

where, C_t= urea concentration at time t, C_o= initial urea concentration

Kinetic Modelling of Solutes other than Urea

Sodium, a potent osmotic regulator of water distribution in the body, can cause side effects such as muscle cramps, symptomatic hypotension, headache, nausea when there is a change in sodium concentration and water shift between intracellular and extracellular space during haemodialysis. Sodium kinetic modelling is thus important to guarantee appropriate manipulation of sodium concentration [27,28]. Petitclerc, et al. [27]; Filippo, et al. [29]; Coli, et al. [30-32] are among researchers that have worked on sodium kinetic modelling to demonstrate how sodium can reduce the side effect during haemodialysis. Few clinical studies have been able to demonstrate the clinical evaluation of the sodium model in reducing hypotension-related morbidity [28]. Modelling of electrolytes such as K+, HCO3- and Ca2+ have been studied by Locatelli F, et al. [30], Fernandez de Canete J, et al. [33], Eloot, et al. [17], Cronin-Fine D, et al. [34] have proven to be essential in feedback control systems and profiled dialysis.

The kinetics of iodine was investigated by Eloot S, et al. [35-37]. Eloot, et al. [35] determined the best dialysis approach. In their work, two–injured patients were treated with povidone-iodine on their open burn wounds and were placed on different haemodialysis strategies such as intermittent dialysis, alternate day dialysis, long and intensive dialysis. The result of their work showed that the best dialysis strategy to remove iodine was obtained by daily long (12h) intensive dialysis. Other researchers on iodine kinetics are

Sprenger, et al. [13] studied the urea and creatinine kinetic models using the single and double pools and concluded in their work that the double pool model is necessary and suitable for simulating creatinine kinetic models, and for describing the kinetics of uric acid, vitamin B12 and inulin during dialysis. The toxin kinetic model for Haemodialysis patients was studied by Spalding EM, et al. [38] to understand the physiological distribution of toxins, their accumulation and removal characteristics. The work employed a model-based design of experiments technique to explain optimal sampling protocol. The result of the work showed that with the technique used, parameters are estimated better using samples collected in the intra-dialytic phase. However, these samples should be collected only towards the end of the post-dialytic phase because post-dialytic phase samples are less informative.

Phosphate kinetics was described by Eloot S, et al. [17], the work showed that phosphate kinetic model is not only governed by diffusion and inter-compartment mass transfer and solute generation, it is also a time-dependent and rapid influx of phosphate into the extracellular space by biochemical processes or mobilization from the bones which constitute a large phosphate reservoir. The work concluded that phosphate concentration almost levels off or even increases during dialysis which might be due to active metabolic processes. A four-compartment model was developed by Spalding, et al. [39] to describe the barrier to phosphate removal during dialysis. The result of their work suggested that the transfer of phosphate from intracellular to extracellular compartment can limit the barrier to phosphate removal during dialysis, however, some complex factors also play a major role. Also, theoretical prediction from the model is that increasing the treatment frequency or duration of treatment can increase the removal of phosphate [40].

Baigent, et al. [32] modelled profiled haemodialysis, a haemodialysis process whereby the rate of water removal and/or the dialysis machine sodium concentration is varied according to predetermined profile, by modelling the intracellular sodium, hollow fibre dialyze and then a method for identification of plasma volume refilling rate from interstitial space as a rate-limiting process. The result of their work was not compared with clinical data from a profiled haemodialysis session. To analyze the accuracy of haemodialysis modelling in the course of treatment and in predicting the effect of the haemodialysis procedure, Ziolko, et al. [9] used mathematical model coefficients that is based on concentration measurement of urea, creatinine and uric acid in the patients' blood and dialysate using one and two-compartment model. There result showed that both models described the concentrations of urea, creatinine and uric acid effectively, however, two-compartment model was more effective but more complicated than the one-compartment model.

In the investigative work of a Cronin-Fine D, et al. [34], the mathematical model was developed to compare solute kinetics in Haemodialysis patients having low body mass index (BMI) with solute kinetics in patients with high BMI. Their study focused on how kinetic modelling can explain why smaller BMI patients a higher mortality risk have than higher BMI patients using a three-pool urea-kinetic model. The categorized BMI are 40kg bodyweight for the small patients, 70 kg for the middle patients and 100kg for large

patients. The result of their work suggested that higher mortality for smaller dialysis patients may be facilitated by higher average toxin concentration, especially for solutes with a low mass-transfer coefficient value.

A two-compartment model, inter-compartment and extra-compartment was developed by Canto, et al. [41], for determining the efficiency of models used for dialysis process analysis by using structural identifiability. The work was based on the determination of some unknown parameters using biological system's behaviour to determine the input-output behaviour in state-space, however, no clinical analysis was carried out.

Intersection of Solute Kinetic Modelling and SDGs

Chronic Kidney Disease has become common disease worldwide affecting almost 850 million people with majority undergoing dialysis treatment [15]. Solute kinetic modelling is an important approach that align with broader global objectives, outlined in the Sustainable Development Goals (SDGs) established by the United Nations. The potential contribution of SDGs in solute kinetic modelling are highlighted as follows:

Good Health and Well-Being (SDG 3): Enhancing quality and precision of hemodialysis treatments, effective solute removal and electrolyte balance will improve patient health outcomes and reduce morbidity and mortality of dialysis patient.

Innovation in Healthcare Technology (SDG 9): Continuous improvement in modeling techniques fosters efficient, cost-effective solutions, innovative methods capable of promoting in healthcare industry.

Reduced Inequalities (SDG 10): Innovative modelling techniques can enable more effective, low-cost, and accessible treatments, that reduce disparities in healthcare, enabling that quality care is available to all patients.

Efficient use of Resources (SDG 12): Haemodialysis solute kinetic modeling contributes to efficient resources usage and sustainable healthcare practices and reduction in environmental impact.

Conclusion

This work explained the importance of various parameters that influence solute kinetic models, such as dialyzer clearance, residual renal clearance, solute generation rate, and compartment effects in predicting, monitoring, and optimizing towards quality haemodialysis treatment. Classification of solutes and their kinetic models were analyzed in this work. SKM has shown as quantitative tool that predicts solute clearance, assess vital treatment parameters, and contribute to improved patient outcome. Also, innovation in SKM is closely related to Sustainable Development Goals (SDGs) through advancing global health, fostering innovation, reducing inequalities, and promoting sustainability. SKM is important tool in achieving effective and efficient haemodialysis treatment that can reduce the mortality of patients with kidney disease.

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