Journal of the Nigerian Association of Mathematical Physics
Volume28, No. 1, **(***November, 2014***), pp275 – 280**

Fuzzy Inference Model on Drug Dosing Requirement for Hypoglycaemic patient with Chronic Kidney Disease

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Abstract

Hypoglycaemia is a condition that causes blood sugar level to drop dangerously low. It mostly shows up in diabetic patients who take insulin. Hypoglycaemia usually occurs in people being treated for diabetes (type 1 and type 2).Chronic kidney disease (CKD) is a long term condition caused by damaged to both kidney. There is no single cause and damage is usually irreversible. Diabetes mellitus is one common cause of CKD.A key goal for diabetic treatment in patient with CKD is rigorous glucose control to prevent end stage renal disease (ESRD).In this work, we proposed fuzzy inference model for determine dosing requirements for hypoglycaemic patient withCKD. The expert system was designed based on four (04) Glucose –Lowering drugs needed for prescription; Acarbose, Metformin, Chlorproamide and Glipizide and CKD classifications. Clinicians choose from list of drug and CKD stage of the patient and the expert system prescribe the drug dosage requirement for that particular drug.

Keywords:chronic kidney disease, drug, fuzzy logic, Hypoglycaemic.

1.0 Introduction

Chronic kidney disease (CKD) is a long term condition caused by damaged to both kidney. There is no single cause and damage is usually irreversible. Diabetes mellitus is one common cause of CKD.Hypoglycaemia is a condition that causes blood sugar level to drop dangerously low. It mostly shows up in diabetic patients who take insulin. Hypoglycaemia usually occurs in people being treated for diabetes (type 1 and type 2). Individuals with pre-diabetes who have insulin resistance can also have low blood sugars on occasion if theirhighcirculating insulin levels are further challenged by a prolonged period of fasting. There are other rare causes for hypoglycaemia. CKD is seen more frequently in older people and therefore is likely to increase in population [1]. Diabetes had been the most common cause of kidney disease worldwide. A key goal for diabetic treatment in patient with CKD is rigorous glucose control to prevent end stage renal disease (ESRD). Diabetes management in CKD population warrants special consideration. Insulin is a renal cleared drug, hence patient who have CKD with reduced glomerular filtration rate (GFR), (<60 mL/min/1.73m^2) frequently have lower insulin requirement. These and other factors contribute to a greater risk for hypoglycaemia among patient with CKD[2].CKD alters the effects of many drug and as a result inappropriate dosing in patients can cause toxicity or ineffective therapy. Dosage of drug cleared renally should be adjusted according to clearance or GFR [3]. Clinician should pay careful attention when considering drug therapies with active or toxic metabolites that can accumulate and contribute to pharmacological effects or adverse drug reaction in patient with CKD [3]. Renal disease interacts with drug in three main ways. Firstly, patients with renal disease may be more vulnerable to a given drug effect (patients susceptibility). Secondly, a drug effect may be exaggerated or attenuated in patients with renal disease (Pharmacodynamics change). Thirdly and most importantly, some drugs have higher steady-rate concentration when given at usual doses to patients with renal diseases (Pharmacokinetics changes).

In this paper, a Fuzzy Inference Model on Drug Dosing Requirement is proposed for Hypoglycaemic patients with CKD (DDRH with CKD) to account for the pharmacokinetic changes that occur in renal disease.The drug dose should be reduced proportionally to the predicted reductionin drug clearance. Increase drugclearance result in lower drug concentrations, while decreased drug clearance result in higher drug concentration and hence greater drug effects. To avoid harm when drug clearance is significantly decreased, the dose of renally cleared drugs should usually be reduced in patients with CKD. There are dosing recommendation for individual drugs which can be found in "Drug Prescribing in Renal failure [4]"

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2.0 Drug Dosing

Estimate of glomeruler filtration rate (GFR) are used to estimate renal function and also renal drug clearance. Some active drug moieties are wholly or partly cleared from the body by the kidneys and this is the physiological rationals for using GFR to estimate drug clearance, serum creatinine is dependent on both creatinine production (equivalent to drug dose) and creatinine clearance (equivalent to renal drug clearance).

Dosage of drugs cleared renally should be adjusted based on the patient renal function (calculated as creatinine clearance or glomerular filtration rate); initial dosage should be determine using published guidelines and adjusted based on patients response [5,6].

The units of drugs dose are amount per unit time;for example 200mg twice daily. For most drugs, prescribing information recommends a standard dose and provides some guidelines on when this should be altered[7]. The advice is necessary imprecise as most drugs have inter-individual variability clearance and response. Having a means to identify when drug dose should be halved or doubled is important, where as 20% change in dose is usually impractical or unnecessary. However there are several drugs for which small changes in dose or concentrations may have an important effect commonly known as a narrow therapeutic index.

Therapeutic index= $\frac{maximumtoxicdose}{minimumeffectdose}$

Drug dosing is a challenging problem in diabetic –CKD patient. CKD can potentially influence the pharmacokinetics of every therapeutic agent. This translates into an enhanced risk for hypoglycaemia, side effects and drug-to-drug interactions. As a consequence, a reduction in dosing and/or frequency of administration is necessary to keep a satisfactory efficacy/safety profile. The concurrent use of multiple drugs is often attended with drug – drug interactions which represent an important category of adverse reactions to drugs [8]. Information on drug interactions is huge in volume in literature and still increasing, it is hardly possible to check potentially dangerous drug combinations completely by manual method, particularly when a patient is administered the multitude of drugs. As aid for the medical practitioners, some computerised drug information systems provide the services of drug- drug interaction checking [9].

Adverse Drug Reaction (ADR) and harmful effects of pharmaceutical excipients imply severe incidences, due to incompatibilities of the drug with medical history. The rate of ADR appearance is extremely high in worldwide hospitals [10].

The primary reason for the success of fuzzy logic in process engineering is the ability to model highly efficient non linear systems for which mathematical models are nonexistent or inefficient in traditional rule based approach knowledge is encoded in the form of antecedent consequent structure. When new data is encountered it is matched to the antecedent clauses of each rule and those rules where antecedent data match are exactly fired, establishing the consequent clauses in the past decade fuzzy logic has proved a wonderful tool for intelligent systemsin medicine. In medicine most medical concepts are fuzzy. The imprecise nature of medical concept and their relationship require the use of fuzzy [11]. It defines exact medical entities as fuzzy sets and provides a linguistic approach with an excellent approximation text.

Fuzzy logic in medicine has two different meanings-wide and narrow. In particular, such key concepts in FLN (Fuzzy Logic Network) as a concept of linguistic variable, canonical form,fuzzy if-then rule, fuzzy quantification, the extension principle, the compositional rule of inference and interpolative reasoning, is not addressed in traditional system.

Based on Zadeh's opinion [12] on fuzzy logic, we may conclude in the broad sense, everything dealing with fuzziness may be called fuzzy logic. Fuzzy logic offers reasoning methods capable of drawing approximate inferences.Much had been written in the 1980s about the role of explanation facilities in medical diagnostic expert systems: MYCIN [13,14] and PUFF [15] were both prototype medical expert systems of interest because of their explanation. However, despite being widely recognized as a useful adjunct to expert systems, explanation facilities have been largely ignored in the health care literature in recent years. This is partly because explanation facilities were first used in diagnostic applications, such as the MYCIN expert system and its derivatives in the 1980s, but the clinical tasks served by expert systems have changed considerably since this time [16 -18]. Currently, expert system tasks are more likely to be used in the determination of drug dosing and drug prescribing or in reminding clinicians to engage in preventive interventions through inoculations. Most prescribing software that was assessed did not offer consistent useful support to pharmacists for making decisions about drug interaction. [19] proposed a fuzzy expert system for improving prescriptionperformance. This system was a foundation view on general drug prescription. Motivated by inappropriate dosing and adverse drug reaction as a result of prescription error,we proposed fuzzy inference model for DDRH patient with CDK to actively assist pharmacist and physician in appropriate dosing adjustment for hypoglycaemic patients with CKD. We employ the recommendation of "drug prescribing in renal failure; dosing guidelines for adults and children, an expert panel, including nephrologists and pharmacist, determined the dose adjustments according to the estimated glomerularfiltration rate (eGFR)."The expert panel determined the range and frequency of administration for each of the medication.

II. Method

A review of existing literature on hypoglycaemic in CKD and its management and fuzzy logic was carried out. Hypoglycaemic Agents Dosing Requirements in patients with CKD were presented which was gotten from *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults,* which was used in our analysis. In the domain of hypoglycaemia in patient with CKD, a fuzzy set*a* in A *(*a universe of discourse) of hypoglycaemic with CKD attributes denoted by x is given as equation (1).

$a = \{(x,\mu_a(x))/\ x \in A\ \mu_a(x) \in [0,1]\}$----------(1)

Where $\mu_a(x)$ is the membership function (MF) of x in a, and μ_a is the degree of membership of x in a in the internal [0,1]. Membership functions are of different types, commonly used MFs are Triangular, Trapezoidal and Gaussian [20]. Triangular MFs has been used extensively in medicine due to its computational efficiency in modelling the human reasoning process.In this work, thefuzzy system is used in the triangular function equation (2), we presented an architecture model for the system for determine dosing requirements in patient with hypoglycaemic in CKD as shown in Figure 1.

$$\mu_a(x) = \begin{cases} 0 & \text{if } x \le b \\ \frac{x-a}{b-a} & \text{if } a \le x \le b \\ \frac{c-x}{c-b} & \text{if } b \le x \le c \\ 0, & \text{if } c \le x \end{cases} \qquad (2)$$

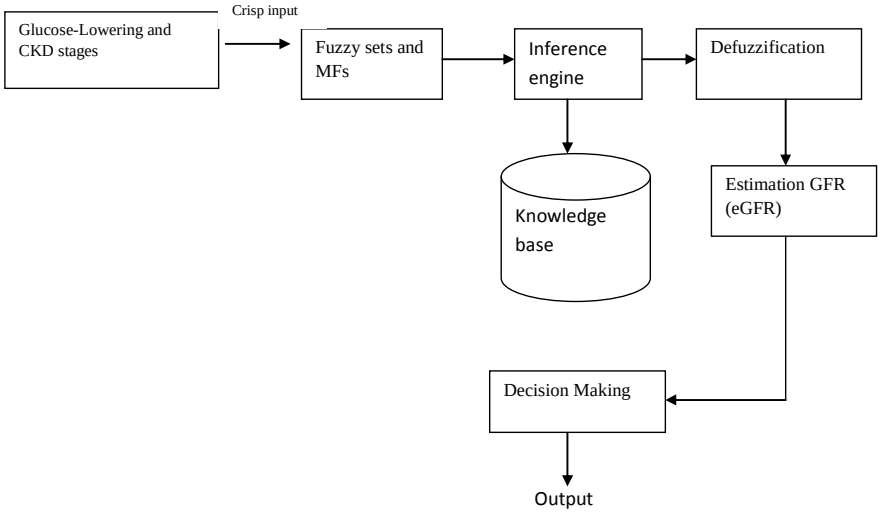

Figure 1: Architecture of the system.

It comprises of knowledge base system, inference engine, decision support module, fuzzy logic. The knowledge base consists of drugs requirements for patients with CKD and its stages. The values of hypoglycaemic patient with CKD is vague and imprecise hence the adoption of fuzzy logic as a means of analyzing these information. These values therefore constitute the fuzzy parameters of the knowledge base. The fuzzy set of the hypoglycaemic patient with CKD is represented with' P' which is defined as P= { p_1, p_2 -----p_n} where p_i represents the jth parameter and n is the total number of parameters (n=4). The inference engine consists of reasoning algorithm, driven by production rules. These rules made use of forward chaining approach of reasoning.

Table1: Usual Dose for hypoglycaemic drug.

Drugs	**Usual Dosage**
Acarbose	75- 300mg daily
Chlorpropamide	250 -500mg once daily
Glipizide	2.5-10mg daily
Metformin	500- 100mg three times daily.

Source:[21]

Table 2: CKD classification

CKD Stages	**Description**	**GFR (ML/ Min/1.73m^2)**
1	Normal/raised	≥ 90
2	Mild	60-89
3	Moderate	30-59
4	Severe	15-29
5	ESRD	< 15

Source: [22]

Table 3: Adjusted Dosing hypogyclyceamic Requirement for CKD Patient

Drugs	Normal/raised CKD-1	Mild CKD-2	Moderate CKD-3	Severe CKD-4	ESRD CKD-5
Metformin	No adjustment	No adjustment	500-850mg/day	500mg/day	Consider carefully
Chlorpropamide	No adjustment	No adjustment	100-125mg/day	To be avoided	To be avoided
Glipizide	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
Acarbose	No adjustment	No adjustment	No adjustment	Avoid if GFR< 25ML/Min	To be avoided

Source: [21]

Table 1 is the usual dosage on hypoglycaemic drug for patients without CKD, which does not require adjustment in dosing regimen. Because hypoglycaemic drugs are renally cleared; hence the need to appropriately adjust drug dosing for patient with CKD based on CKD stages; the classification of CKD is shown on Table 2 while the adjusted dosage is reflected on Table 3. Table 3 shows the different glucose lowering drugs, CKD stages;which are Normal/raised, Mild, Moderate, Severe and ESRD. The various drugs are adjusted in accordance to the CKD stages.

III. Results and Discussion

In designing our proposed model on drug dosing requirement for hypoglycaemic patient with CKD, we design a system which consists of four (04) Glucose –Lowering drugs needed for prescription; Acarbose, Metformin, Chlorproamide and Glipizide.

The knowledge base consists of four (04) drugs(parameters) mentioned earlier and CKD classifications. The values are vague and imprecise hence the adoption of fuzzy logic as a means of analyzing these data.The operational procedure of the proposed model is represented in Figure 2. The sets of drugs and CKD stages are fed into the system. Theclinicians choose the drug and the CKD stage of the patient and prescript the drug dosage requirement for that particular drug.

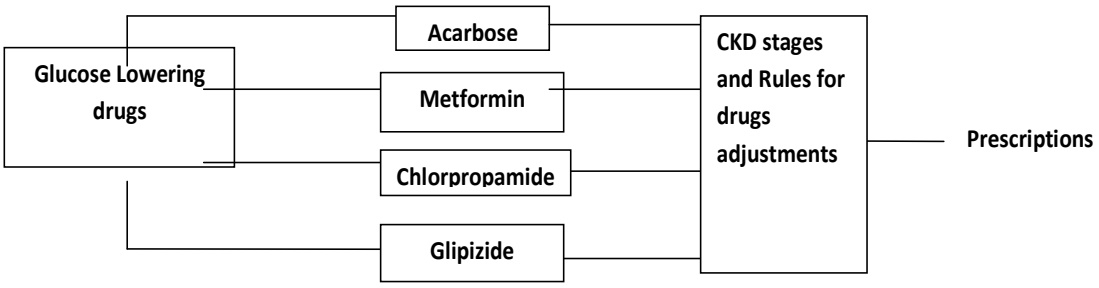

Figure 2: Operational procedure of DDRH with CKD.

Defuzzification

Defuzzification is interpreting the membership degree of the fuzzy sets into a specific decision or real value.

Base on the input variables, the fuzzy rule for drug dosage adjustment for hypoglycaemic patient with CKD (DDRH with CKD) is given as follows;

For Metformin (MET);

Rule 1: if GFR= 60 ≥ 90,Then No adjustment of Metformin

Rule 2: if GFR = 30 ≥ 59, The adjust Metformin dosage to 500mg -850mg/daily

Rule 3: if GFR = 15 ≥ 29, Then adjust Metformin dosage to 500mg daily

Rule 4: if GFR < 15, Then consider Metformin dosage carefully.

Rule for Chlorpropamide (CHL);

Rule 1: if GFR = 60, ≥ 90 Then No dosage adjustment for chl

Rule 2: if GFR = 30 ≥ 59, Then adjust chl dosage to 100mg-125mg/day

Rule 3: if GFR = 15 ≥ 29, Then avoid chl

Rule 4: if GFR < 15, Then avoid chl.

Rule for Glipizide (GLI)

Rule 1: if GFR < 15 ≥ 90, The No dosage adjustment for Gli

Rule for Acarbose (ACA);

Rule 1: if GFR = 30 ≥ 90, Then No dosage adjustment for Aca

Rule 2: if GFR < 30,Then avoid Aca.

Table 4: Fuzzified data of Adjusted Dosing hypoglycaemic Requirement for CKD Patient

CKD Stages	DRUGS			
	Metformin	**Chlorpropamide**	**Glipizide**	**Acarbose**
Normal/raised CKD-1	0.55- 0.1	0.55-0.1	0.78-0.1	0.78-0.1
Mild CKD-2	0.55-0.1	0.55-0.1	0.78-0.1	0.78-0.1
Moderate CKD-3	0.55-0.23	0.82--0.80	0.78-0.1	0.78-0.1
Severe CKD-4	0.55	0.1	0.78-0.1	1.0
ESRD CKD-5	0.1	0.1	0.78-0.1	1.0

Table 5: Mean Value of Fuzzified data of Adjusted Drug Dosing hypoglycaemic Requirement for CKD Patient

CKD STAGES	DRUGS			
	MET	**CHL**	**GLI**	**ACA**
CKD1	0.33	0.33	0.44	0.44
CKD2	0.33	0.33	0.44	0.44
CKD3	0.39	0.81	0.44	0.44
CKD4	0.55	0.1	0.44	1.0
CKD5	0.1	0.1	0.44	1.0

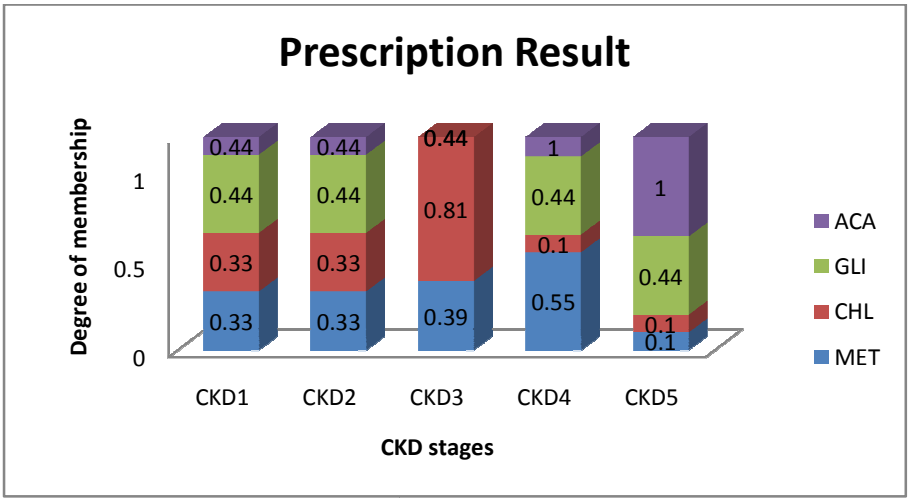

Figure 3: A graph showing the prescription result.

The graph in Figure 3, shows the stages of CKD classification with the membership function needed for various drug dosing adjustment requirement for hypoglycaemic patient with CKD

3.0 Conclusion

The proposed Fuzzy Inference Model on Drug Dosing Requirement for Hypoglycaemic patients with CKD (DDRH with CKD) was designed using the rule based approach; knowledge is encoded in the form of antecedent consequent structure. Our system provides expert guide to clinicians on drug dosing adjustment requirement necessary to keep a satisfactory efficacy/safety profilefor hypoglycaemic patients with CKD

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