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Glycemic Variability Among Type 2 Diabetes Patients With Chronic Kidney Disease (CKD) Using Continuous Glucose Monitoring: A Study From A Tertiary Care Hospital

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Abstract

Background and objectives: HbA1C which is considered widely to be the gold standard for assessing glucose control is not a true reflection of average glucose, in CKD patients with Diabetes. Hence current study is aimed to assess glycemic variability among Patients with CKD using a continuous glucose monitoring system (CGMS) and correlate the effect of factors such as age,sex,BMI, eGFR and effect of antidiabetic medications.

Methodology: A cross-sectional study was conducted among a total of 60 subjects- equal number of patients with diabetic and nondiabetic CKD for a period of 18 months, all the study subjects were subjected to Continuous Glucose Monitoring and the data was analysed.

Results: Subjects with non-diabetic CKD had majority of the blood glucose readings i.e., 90.37% in target range (70-150mg/dl), whereas Diabetic CKD patients had only 79.17% readings in target range. The mean HbA1C measured by HPLC method was

lower than the mean HbA1c estimated by CGMS. Among various risk factors, declining eGFR was associated with a significant risk of increased glycemic variability..

Conclusion: A higher incidence of glycemic variability in Diabetic CKD patients and hence higher oxidative stress, warns against higher risk of microvascular complications which have to be taken care during further follow ups and use of newer modalities such as CGMS, to individualize antidiabetic drug doses on the basis of each patient's glycemic response and patterns.

Keywords: Glycemic variability, continuous glucose monitoring, CKD, Type 2 DM

Introduction

Diabetes mellitus is the most common cause of chronic kidney disease(CKD) in the world, leading to multiple complications including end-stage renal disease, cardiovascular disease, infection and death[1]. It is the result of diabetes as well as associated comorbidities such as hypertension and obesity. Approximately 20-30% of patients with diabetes have renal impairment, classified as moderate to severe CKD (GFR<60 ml/min/1.73m^2)[(2)]. CKD in setting of diabetes or diabetic kidney disease, manifests clinically as albuminuria, reduced glomerular filtration rate(GFR) or both[1].

Glycemic variability in diabetics refers to variation around the mean blood glucose or fluctuations in blood glucose levels between high/peak and low/nadir levels. Chronic complications of Diabetes, including microvascular and macrovascular changes, are the leading cause of diabetes-related death and disability. Preventing or delaying the development of

these complications is very important. Several studies indicated that glycemic variability seems to be an independent cardiovascular risk factor and has more deleterious effects on endothelial function compared to sustained hyperglycemia, especially due to oxidative stress activation [3,4].

DM is a metabolic disease that can lead to renal failure, and renal failure increases the need for insulin in diabetic patients. The accumulation of uremic toxins and increased parathyroid hormone levels in patients with chronic renal failure (CRF) causes insulin resistance in tissues, particularly skeletal muscle tissues. This has been attributed to damage in the process after insulin binding to its receptors, which disturbs glucose metabolism and glycogen production.

Insulin secretion is also reduced in patients with CRF, which appears to be due to metabolic acidosis, elevated levels of parathyroid hormone, and decreased level of vitamin D.

Although insulin resistance increases the insulin requirement, decreased insulin degradation reduces the need for administration of insulin or even resolves it in patients with type 2 diabetes. This may increase the risk of hypoglycemia.

Hence the increased glycemic variability in diabetics with CKD can be attributed to a multitude of factors which include changes in insulin signalling, glucose transport, accumulation of uremic toxins, inflammatory mediators and oxidative stress, inducing insulin resistance, decreased renal gluconeogenesis, altered metabolism of medications and decreased insulin clearance.

CKD in patients with Diabetes is associated with a number of serious complications, including increased incidence of cardiovascular disease, hyperlipidemia, anemia and metabolic bone disease. Glycemic control is essential to delay the onset of complications from diabetes and progression of CKD, and it can be challenging for even the most experienced physician. Blood sugar control in those with CKD adds another level of complexity. Though, overall objective of management of type 2 diabetes is to achieve and maintain blood glucose control and reduce the risk of long-term complications and many studies though show that modern management with intensive glycemic control can limit, delay or even prevent the chronic complications of diabetes, such intensive diabetes treatment could be associated with an increased risk of hypoglycemia in individuals with CKD.

Hypoglycemia has been a common side effect of diabetes therapy, resulting in a lack of adequate cerebral glucose supply, leading to a range of neurogenic and neuroglycopenic symptoms. Consequences of hypoglycemia can cause injury, myocardial infarction, seizure, stroke or death, and are greatest in those who are frail and elderly, with erratic eating habits, on insulin and sulfonylureas, and with CKD. It requires detailed knowledge of which medications can be safely used and how kidney disease affects metabolism of these medications. In addition, the glycemic target needs to be individualized for each patient, acknowledging that our ability to interpret the data can be altered in the setting of kidney disease.

HbA1c (A1c) which is widely considered as the gold standard in assessing glucose control in diabetes, however is not a true reflection of average glucose in Diabetic Kidney Disease. In CKD patients there are various factors which could lead to false and misleading values of HbA1c[4], among the factors that lead to falsely low HbA1c values are: hemolysis, reduced erythrocytes lifespan, iron deficiency, repeated transfusions, erythropoiesis stimulating agents[5]. Falsely high HbA1c levels are induced by hemoglobin carbamylation[6,7]. Several analytes, including glucose, A1c, fructosamine, glycated albumin and 1,5-anhydroglucitol are available for the evaluation of glycemia, but it does not reflect short-term oscillations in blood glucose on a smaller scale of hours to days. No two individuals with diabetes are the same with respect to glycemic control i.e., they can have same average A1c value with markedly different overall glycemic controls due to excursions in glucose levels. It should be noted that despite the decreased insulin secretion and impaired tissue sensitivity to insulin that occurs in patients with CRF, most nondiabetic CRF patients do not have hyperglycemia unless they are genetically predisposed. Hence the current observational study is designed to study the short term oscillations of glucose levels for a period of 5 days among CKD patients by using continuous glucose monitoring (CGM) as it uses glucose as a more important clinical tool, for a more definitive understanding of glycemic

variability, thus foreseeing the complications and better management among high risk individuals.

Materials & Methods

Source Of Data: CKD Patients (Diabetic and nondiabetic) attending Out-patients and inpatient to the department of General Medicine at Rajarajeswari Medical College and Hospital, Bengaluru, fulfilling the inclusion and exclusion criteria were included in the study after taking informed consent from them.

Study Duration : 18 months

Study Design : Hospital based cross sectional observation study

Type Of Sampling : purposive

Sample Size : 60 (30 diabetic and 30 nondiabetic CKD patients)

Sample Size Calculation

Considering the 96.0% prevalence of hypoglycaemia among diabetic patients as per literature in India, with 95% confidence interval and absolute error (L) of 36, the total sample size of 60 was obtained to study the glycemic variability. The formula used was $n=z^2 (pq/L^2)$, where, z=1.96 at 95% confidence interval, p = estimated prevalence (96.0%), q=100-p (4.0%) and L = permissible error (absolute error of 6%, the total sample size of 60 was considered for the study. The sample size of 41 was obtained. Considering the non-response rate of 10.0%, 41+4≈ 45 was the minimum sample size. For the convenience of analysis as diabetic and nondiabetic CKD was included in the present study a minimum of 60 were selected.[(113)]

Inclusion Criteria:

1. Age > 18 years
2. Diagnosed CKD (Either Kidney damage or GFR<60ml/min/ 1.73m^2 for ≥ 3 Months -NKF KDIOQI guidelines)

Exclusion criteria:

1. Subjects diagnosed with type 1 Diabetes Mellitus
2. Subjects who are fasting.
3. Pregnancy and lactation
4. Critically ill patients
5. Patients who do not give consent

Ethical Issues And Ethical Committee Clearance [Annexure-1]

The ethical issues were discussed and approved by the Institutional Ethics Committee of Rajarajeswari Medical college and Hospital, Bangalore.

Written informed consent was taken prior to the recruitment of patients into the study & relevant details regarding the purpose, investigations to be carried out, study procedure& potential hazards of the study was explained to the patients in their own language.

Confidentiality was maintained.

ICMR guidelines were strictly adhered to, during the conduct of the study.

Informed Consent [Annexure-1]

Patients were explained about the study procedure and importance of the study in their own language of understanding and written informed consent was taken from them.

Methods Of Data Collection: Case Record Form (Crf)Annexure-2]

- Patients with known case of diagnosed CKD – both diabetic and nondiabetic were taken for the study
- Informed consent was taken from the patient.
- A semi-structured and pre-tested questionnaire consisting of baseline data which included the details on medical history including conventional risk factors, anthropometric measurements including BMI, clinical examinations and relevant investigations was used to collect the data
- After obtaining the written informed consent, detailed clinical history was taken from patients as per the proforma.
- All the patients were examined and subjected to relevant investigations that included the following:

a. Blood routine (Hb , PCV , TC , DC , ESR, Platelet, Peripheral smear)

b. HbA1c measured by HPLC method

c. Blood urea

d. Serum Creatinine

e. Serum electrolytes

f. Liver function tests

g. Fasting lipid profile

h. Urine routine

i. ECG

j. Fundoscopy

k. Echocardiography (if clinically indicated)

- eGFR was calculated using the abbreviated MDRD equation and correlated accordingly
- All the study subjects were subjected to Continuous Glucose Monitoring using CGMS device-iPro2from Medtronic, approved by FDA. A small sensor was inserted intradermal onto the arm of the patient with a reader attached externally for 5 days duration. The patients were then asked to do their normal daily activities.5 days later the sensor was removed. The Continuous Glucose Monitoring uses the interstitial fluid sample and records the glucose levels every 15 mins and the data was collected for a whole 24 hour period and a series of such data was collected for a period of days.
- The estimated HbA1c was calculated according to the formula : eHbA1c= (3.38 + 0.02345 × [mean glucose in mg/dL]

Statistical Analysis:

Study population were divided into 2 groups based on the diabetic status. The collected data were entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test or Fischer's exact test** (for 2x2 tables only) was used as test of significance for qualitative data. The continuous data viz., age, BMI, FBS, HbA1c, Serum Creatinine, Blood Glucose, fasting lipid profile values recorded at the time of examination were expressed in means and standard deviations. The discrete data viz., number of episodes of hypoglycaemia and hyperglycemia among the subjects were expressed in proportions. **Independent t test** was used as test of significance to identify the mean difference between two quantitative variables. **Paired t test** is the test of significance for paired data. Correlation analysis was performed to correlate the variabilities in glucose level with factors like age, sex, BMI, Egfr, stage of CKD, and type of antidiabetic medication used.

P value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs such as bar diagram, Pie diagram.

Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

Results

In the present study out of 60 patients, majority of patients- 35 patients (58.3%) had stage 3 CKD, followed by 15 patients (25%) with stage 2, and 10 patients (16.7%) with stage 4 CKD. P Value among CKD with DM and CKD without DM with respect to stage of CKD was found to be 0.392, there was no statistically significant difference found between subjects chosen in our study among the two groups (Table 1).

The mean HbA1C by conventional – HPLC method among CKD with DM was 5.9 and that of nondiabetic CKD was 4.7, whereas the mean HbA1C estimated by CGMS was 6.4 and 5.1 respectively among subjects with diabetic and nondiabetic CKD (Table 2).

There was a statistically significant difference found between CKD with DM and CKD without DM with respect to % of blood glucose readings above 150mg/dl, below 70mg/dl and in target range. Subjects with non-diabetic CKD had majority of the blood glucose readings in target range (70-150mg/dl) with a mean of 90.37%, whereas Diabetic CKD patients had lesser glucose readings in target range with a mean of 79.17%. Subjects with diabetic CKD had both episodes of hypo and hyperglycemia with a mean of 8.93% readings above 150mg/dl and 12.07% readings below 70mg/dl. Subjects with nondiabetic CKD had several episodes of hypoglycaemia with a mean of 7.90% blood glucose readings below 70mg/dl and rarely epi (Table 3).

In the present Out of 30 diabetic CKD patients receiving dose adjusted antidiabetic medication as per EGFR and HbA1C levels, 7 patients were on Insulin , 7 patients on sulfonylureas, 6 patients on DPP4 inhibitors, 4 patients on thiazolidinediones, 3 patients on Biguanides, and 3 patients did not require any antidiabetic medication (Table 5).

In the present study among Diabetic CKD patients who were on antidiabetic medication with respect to HBA1C as measured by standard method priorly, the glycemic variation with respect to antidiabetic medication received was as shown in the table as shown above respectively (Table 5).

There was a statistically significant difference found between type of antidiabetic medication used and % of blood glucose readings above 150mg/dl, below 70mg/dl and in target range (70-150mg/dl).

1. In patients with early stages of CKD- stage 1 and 2, on biguanides-dose adjusted with no contraindications, had a mean of 91% of the blood glucose readings in target range.
2. In CKD patients who were on low dose sulfonylureas, a mean 75% of blood glucose readings were in target range, a mean of 16% blood glucose readings were in hypoglycemic range and 9% in hyperglycemic range respectively. Glycemic variation with relatively higher episodes of hypoglycaemia was observed.
3. In patients on DPP4 inhibitors dose adjusted with respect to EGFR , about 91% of blood glucose readings were in target range.
4. Patients of advanced stages of CKD-stage 3b and stage 4, who were on insulin therapy, had poor glycemic control, with about 65% of blood glucose readings in target range and a similar range of blood sugar levels in hypo and hyperglycemic range blood sugar levels with a mean of 17%respectively.
5. In a very few proportion of patients with early stages of CKD, with no cardiac contraindications, who were on thiazolidinediones - 90% of blood glucose readings were in target range sodes of hyperglycemia with a mean of 1.8% readings above 150mg/dl.

Table 1: Distribution of subjects according to stage of CKD

	CKD		Total
	With DM	Without DM	
2	8	7	15
	26.7%	23.3%	25.0%
3a	10	7	17
	33.3%	23.3%	28.3%
3b	6	12	18
	20.0%	40.0%	30.0%
4	6	4	10
	20.0%	13.3%	16.7%
Total	30	30	60
	100.0%	100.0%	100.0%

Table 2: Mean HbA1C in the study population

	GROUP	Mean	SD
HBA1C	CKD with DM	5.976667	.5952011
	CKD without DM.	4.790000	.4656105

HBA1C as estimated by CGMS	CKD with DM	6.480000	.6769098
	CKD without DM.	5.116667	.5004021

Table 3:- Comparison of glycemic variation- % of blood glucose readings above 150mg/dl, below 70mg/dl and in target range between two groups

	GROUP	Mean	SD	P value
% of blood glucose readings above 150mg/dl	CKD with DM	8.93	6.005	<0.01
	CKD without DM.	1.80	1.669	
% of blood glucose readings below 70mg/dl	CKD with DM	12.07	7.956	0.012
	CKD without DM.	7.90	3.836	
% of blood glucose readings in target range(70-150)	CKD with DM	79.17	12.900	<0.01
	CKD without DM.	90.37	3.459	

Table 4 : Distribution of DKD patients with respect to treatment received by patient for diabetic control

Antidiabetic medication used- dose adjusted as per eGFR	Number of patients	Percentage %
Not requiring any medications	3	10
Insulin	7	23.33
Biguanides	4	13.33
Sulfonylureas	7	23.33
Thiazolidinediones	3	10
DPP4 inhibitors	7	23.33

Table 5: Comparison of % of blood glucose readings above 150mg/dl, below 70mg/dl and in target range according to medication among CKD with DM subjects.

	% of blood glucose readings above 150mg/dl		% of blood glucose readings below 70mg/dl		% of blood glucose readings in target range(70-150)	
	Mean	SD	Mean	SD	**Mean**	**SD**
Biguanides	4	1	4	3	91	2
DPP4 inhibitors	5	2	5	2	91	2
Insulin-dose adjusted	17	6	17	8	65	12
Not on any medication	5	1	19	2	75	3
sulfonylureas	9	5	16	7	75	11
thiazolidinediones	6	2	4	5	90	4
P Value	**0.01**		**0.01**		**0.01**	

Discussion

Glucose homeostasis and insulin metabolism are complex in patients with Chronic kidney disease with or without Diabetes. Factors like accumulation of uremic toxins, excess visceral fat, chronic inflammation, oxidative stress, metabolic acidosis, and vitamin D deficiency are responsible for increased insulin resistance whereas decreased renal gluconeogenesis, decreased insulin clearance and deranged metabolic pathway are associated with increased risk of hyoglycemia. These Glycemic variations are responsible for oxidative stress and end-organ damage like cardiovascular complications and progression of Kidney disease. Hence in the present study the glycemic variation was studied among patients of chronic kidney disease.

In diabetic patients, chronic kidney disease (CKD) requires special attention due to the multitude of factors that determine glycemic variability. In addition to factors responsible for insulin resistance in CKD, they have pre-existing insulin resistance and insulin deficiency, and also are exposed to a higher risk of hypoglycaemia due to altered metabolism of antihyperglycemic drugs and insulin. Hence accounts to a high risk of both hyperglycemia and hypoglycaemia as compared to that of non-diabetic CKD. Both high and low glycemic levels are associated with increased morbidity and shortened survival in this group of patients.

Conventional methods like FBS, PPBS and HbA1c only record one time sugar levels , and does not record the glycemic variations. Currently, all available glycemic biomarkers, including A1C, have limitations in the setting of DKD. We aimed to assess glycemic variability in patients with CKD and type 2 diabetes mellitus (T2DM) using a continuous glucose monitoring system (CGMS) and identify the factors that affect the glycemic variability.

In the present study, the outcome observed indicated that diabetic patients with CKD had higher glycemic variability compared to nondiabetic CKD. Among 60 CKD patients, equal number of diabetic and

nondiabetic individuals, with no statistically significant difference in age, sex, BMI, comorbidities, habits, lipid profile, eGFR, stage of CKD, were been studied.

The patients with nondiabetic CKD had an average of 90.37% of blood glucose readings in target range, with several hypoglycemic episodes, about 7.90% readings in hypoglycemic range, with relatively rare hyperglycemic episodes with an average of 1.86%. In comparison Patients with Diabetic CKD had only 79.17% of blood glucose readings in target range, they had higher glycemic variability with 12.07% of blood glucose readings in hypoglycemic and 8.93% in hyperglycemic range respectively.

Similar results were observed in a study done by Moen et al., on the frequency of hypoglycemia and its significance in CKD, in which a retrospective cohort analysis of nearly 2,44,000 patients with and without DM showed a higher frequency of hypoglycemic events in diabetic patients with chronic kidney disease (CKD) (defined by an eGFR<60 ml/min per 1.73 m^2) when compared with those without diabetes. Among patients with DM, the rate of hypoglycemia (blood glucose <70 mg/dl) was 11/100 versus 6/100 patient-among patients without diabetes, respectively.[10]

Also a study done by Dede et al and his colleagues on the prevalence of insulin resistance in nondiabetic nonobese patients with chronic kidney disease in which insulin resistance was measured by HOMA-IR, demonstrated that HOMA-IR was significantly higher in patients with CKD than in controls (P<.001) and though insulin resistance was present in patients with nondiabetic CKD, only a few individuals with genetic predisposition had hyperglycemic range blood sugars.[11]

Our study showed that among patients with diabetic CKD the factors like age, sex, BMI did not have any significant correlation with glycemic variability.

EGFR and stage of CKD had positive correlation. With decreasing EGFR and increasing stage of CKD, there was increase in the glycemic variation.

In the study done by Ahmad et al on hypoglycaemia in patients with type 2DM and CKD, out of 81 participants studied the median rate of hypoglycemic episodes was 6.3 and it had an inverse correlation with eGFR and no correlation with age, sex, BMI, which was similar to our study.[12]

Similarly a study done by Tong et al, on Association of various glycemic variability indices and vascular outcomes in type-2 diabetes patients, showed no correlation between age and sex, with glycemic variability and vascular outcomes [13].

In our study the HBA1C measured was lower than that estimated by CGMS among patients of diabetic CKD. This falsely low HBA1C level could be correlated with the lower mean Hb levels and shortened RBC survival present in CKD patients. A prospective cohort study done by Agarwal et al., which assessed the relationship between HbA1C and blood glucose in various stages of CKD, including ESRD also showed that after up to 10 years of follow-up, there was a strong inverse relationship between HbA1C and declining kidney function.(125)Also a study done by vos et al., and his colleagues demonstrated that as the EGFR decreases, erythrocyte survival time becomes shorter and A1C values can be lower independent of blood glucose levels[8].

In the present study, 13.33% patients with early stages of CKD were on metformin and had good glycemic control with a mean of 91.1% blood glucose readings in target range. 23.3% patients were on DPP4 inhibitors, had good glycemic control with an average of blood glucose readings in target range. Even though thiazolidinediones are nearly completely metabolized by the liver, due to concerns of refractory fluid retention, higher BP, congestive heart failure, and increased fracture risk that have been observed with this medication, Only 10% of patients were on this medication, and had a good glycemic control with an average of 90% of blood glucose readings in target range. In 23.3% patients who were on low dose sulfonylureas, higher glycemic variation was observed with only 75% of blood glucose readings in target range, the number of blood glucose readings in the hypoglycemic range was higher with a mean value of 16%. 23.3% Patients, in later stages of CKD, who were on Insulin therapy, had poor glycemic control with only about 65% of blood glucose readings in target range.

A similar study done by busch et al., on Glycaemic control and antidiabetic therapy in patients with diabetes mellitus and chronic kidney disease, antidiabetic treatment patterns were highly variable with a remarkably high proportion of more than 50 % receiving insulin-based therapies. Roughly one

quarter of the patients with DM were treated with an antidiabetic diet regimen only (24.2 %), or received oral antidiabetic drugs, but no insulin (25.5 %). The majority was treated with insulin only (41.8 %) and a small group was on insulin and oral antidiabetic agents (8.4 %). The metformin alone group showed the lowest HbA1C of 6.6 % and the highest eGFR (56 ± 18 mL/min/1.73 m^2). The highest levels of HbA1C were found in the small number of patients treated with insulin and sulfonylureas 7.8 % followed by patients who were treated with insulin and DPP-4 inhibitors having an HbA1C of 7.6 %. These two groups had the lowest average eGFR levels (42 ± 12 and 41 ± 12 mL/min/1.73 m^2, respectively)[14].

A study done by Tuttle et al, also showed that hypoglycemia is consistently a primary treatment concern with the sulfonylurea and meglitinide classes of medications but assumes particular importance in the setting of CKD[15].

Also a study done by Snyder et al, and Bern et al comparing type 1 diabetic patients with and without DKD demonstrated that clearance is reduced for both regular insulin and insulin lispro; however, the effect of regular insulin was also impaired in patients with DKD[(100)]. Because specific insulin preparations have not been well studied in CKD and individual patient needs vary substantially, no definitive guidelines exist for insulin dose adjustments on the basis of eGFR. Thus, a higher dose of regular insulin may be required, despite lower clearance in patients with kidney disease. Because of the lack of evidence for many of the oral and noninsulin injectable antihyperglycemic agents, however, insulin therapy is a mainstay of therapy in patients with advanced CKD.

A study done by Beck et al showed that use of CGM in glycemic management resulted in improved glycemic control[16].

References

1. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care. 2014 Oct;37(10):2864–83.
2. Huang ES, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients: the diabetes and aging study. Diabetes Care. 2011 Jun;34(6):1329–36.
3. Siegelaar SE, Holleman F, Hoekstra JBL, DeVries JH. Glucose variability; does it matter? Endocr Rev. 2010 Apr;31(2):171–82.
4. Monnier L, Colette C. Glycemic variability: should we and can we prevent it? Diabetes Care. 2008 Feb;31 Suppl 2:S150-154.
5. The New KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and CKD - PubMed [Internet]. [cited 2020 Apr 23]. Available from: https://pubmed.ncbi.nlm.nih.gov/17170547
6. Alice Y.Y. Cheng and Lawrence A. Leiter. Cardiovascular risk and glycemic control. CMAJ April 28, 2009 180 (9) 907-908
7. Johnson EL. Glycemic variability in type 2 diabetes mellitus: oxidative stress and macrovascular complications. Adv Exp Med Biol. 2012;771:139–54.
8. Vos FE, Schollum JB, Coulter CV, Doyle TC, Duffull SB, Walker RJ. Red blood cell survival in long-term dialysis patients. Am J Kidney Dis. 2011 Oct;58(4):591-8.
9. Modi GK, Jha V, et al. The incidence of end-stage renal disease in India: a population-based study. Kidney Int. 2006 Dec;70(12): 2131-2133
10. Moen MF,Zhan M, Hsu VD, Walker LD, Einhor n LM, Seliger SL, Fink JC: Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol 4: 1121–1127, 2009pmid:1942356.
11. Sit D, Kadiroglu AK, Kayabasi H, Yilmaz ME. The prevalence of insulin resistance in nondiabetic nonobese patients with chronic kidney disease. Adv Ther. 2006 Nov-Dec;23(6):988-98. doi: 10.1007/BF02850219. PMID: 17276966.
12. Iram Ahmad, Leila R. Zelnick, Zona Batacchi, Nicole Robinson, Ashveena Dighe, Jo-Anne E. Manski-Nankervis, John Furler, David N. O'Neal, Randie Little, Dace Trence, Irl B. Hirsch, Nisha Bansal and Ian H. de Boer. CJASN June 2019, 14 (6) 844-853
13. Tong L, Chi C, Zhang Z. Association of various glycemic variability indices and vascular outcomes in type-2 diabetes patients: A retrospective study. Medicine (Baltimore). 2018

May;97(21):e10860. doi: 10.1097/MD.0000000000010860. PMID: 29794785; PMCID: PMC6392700.

14. Busch, M., Nadal, J., Schmid, M. *et al*. Glycaemic control and antidiabetic therapy in patients with diabetes mellitus and chronic kidney disease – cross-sectional data from the German Chronic Kidney Disease (GCKD) cohort. *BMC Nephrol* 17, 59 (2016). https://doi.org/10.1186/s12882-016-0273-z
15. 1Tuttle KR : Back to the future: Glomerular hyperfiltration in the diabetic kidney. Diabetes 66: 14-16, 2017pmid:27999101
16. Beck RW, Riddlesworth TD, Ruedy K, Ahmann A, Haller S, Kruger D, et al. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial. Ann Intern Med. 2017;167(6):365–74.