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GLYCEMIC VARIABILITY STUDY USING CGMS IN PATIENTS WITH TYPE 2 DIABETES AND CHRONIC KIDNEY DISEASE

ABSTRACT

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CRAIOVA 2013

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Introduction

Diabetes is no doubt one of the most important health problems of the 21st century. This is the fourth cause of death in most high-income countries and there is substantial evidence that make us say that diabetes has become a disease with pandemic evolution. Glycemic control in these patients seems to be the key factor in reducing cardiovascular morbidity and mortality.

Glycemic variability has become a major concern over the years due to evidence gathered regarding its impact on the risk of complications of diabetes.

Even though there is still no method of "gold standard" for assessing glycemic variability, measurement of several indices using continuous glucose monitoring (CGM) can be a useful tool that allows efficient discrimination between sustained chronic hyperglycemia and acute glucose fluctuations.

Taking into account the many factors that influence glycemic control in these patients, and that HbA1c and blood glucose self-monitoring do not detect all dynamic variations glucose, we considered that evaluation using continuous glucose monitoring system (CGMS) can make a more accurate assessment of metabolic status in these patients.

Keywords: continuous glucose monitoring system, glycated hemoglobin, glycemic variability, type 2 diabetes

I.SYNTHESIS OF THE MAIN PARTS OF THE THESIS

I.1.The current stage of the domain of knowing

I.1.1.Glycemic variability

Glycemic variability appears to have most damaging effects on diabetic complications compared with sustained hyperglycemia modifying activation of oxidative stress. Glycemic variability was considered an independent risk factor for cardiovascular complications of diabetes..

Quantifying fluctuations in blood glucose (by assessing glycemic variability, postprandial blood glucose and glycemic excursions) predicts macrovascular damage better than glucose average.

Some researchers have identified several important associations between postprandial glucose excursions and known risk factors for atherosclerosis and suggested that postprandial glucose excursions are independently related to carotid intima-media thickness and may contribute to the development of atherosclerosis in patients with type 2 diabetes independent of other risk factors.

Continuous glucose monitoring provides information about the direction, magnitude, duration and causes fluctuations in blood glucose levels.

Intensive versus conventional glucose monitoring of blood glucose defined as 3-4 times per day measurement, continuous monitoring provides a much higher perspective of glucose levels throughout the day and comparing glycemic curves between two consecutive days.

Taking into cosideration this I considered that using CGMS in patients with type 2 diabetes and chronic kidney disease provides new insights into the assessment of glycemic variability in these patients with evidence of periods of sustained hyperglycemia and acute glucose fluctuations.

I.1.2.Biomarkers of glycemic control

Glycated hemoglobin (HbA1c) is considered the best biomarker, an indicator of glycemic control in the last 2-3 months.

Fructosamine is part of a family of glycosylated proteins and reflects the average blood glucose in the last 2-3 weeks.

Glycated albumin fill the gap of time between self-monitoring and HbA1c glucose meter by about a month.

1-5-anhidroglucitol (1-5 AG), a monosaccharide with a structure similar to that of glucose has been proposed as a marker for postprandial hyperglycemias.

I.1.3.Methods to quantify the glycemic variability - CGMS - Continuous Glucose Monitoring System

Continuous glucose monitoring system (CGMS) is a continuous record of interstitial glucose first approved by the FDA in June 1999.

CGMS measures the amount of interstitial glucose every 5 minutes - continuous - 3-7 days depending on the type of device. Calibration requires 6-12 hours by conventional monitoring of blood glucose.

I.1.4. Glucose metabolism disorders in chronic kidney disease

Most of of patients with CKD in advanced stages have normal fasting glucose but develop abnormal glucose curve after exogenous glucose load.They have hyperinsulinism - before and after glycemic stimulus - and hyperglucagonemia, and manifestations labeled uremic diabetes. In nondiabetic patients with end-stage renal disease, insulin resistance is manifested by mild fasting hyperglycemia and abnormal glucose tolerance tests during the administration of oral or intravenous glucose load. Patients with CKD, associated various changes in carbohydrate metabolism and insulin. Insulin requirements presents a biphasic course in patients with diabetes and chronic kidney disease.

Patients with diabetes mellitus undergoing hemodialysis have a high mortality rate, mainly attributed to cardiovascular disease, these patients have a worse prognosis than non-diabetic subjects

With the beginning of hemodialysis, insulin requirement changes due to improved insulin sensitivity and hepatic metabolism.

Although many studies have shown that poor glycemic control directly determined macrovascular complications with decreased survival, a number of articles have reported that increased levels of glucose average and HbA1c were not associated with increased mortality in hemodialysis patients.

Exposure to glucose peritoneal dialysis fluid and its variable absorption from the peritoneum are potential factors responsible for the variability of blood glucose peritoneal dialysis subjects.

The glycemic variability in PD patients with diabetes may be a consequence of variable absorption of glucose from the peritoneum secondary to diabetic autonomic neuropathy.

So far, glycemic variability was quantified only through a limited number of indicators, thus influence peritoneal dialysis on glycemic variability was not assessed in detail.

I.2.PERSONAL RESEARCH

I.2.1.Aim and Objectives

The aim of the current study is to demonstrate that glycemic variability assessment using CGMS in patients with type 2 diabetes and chronic kidney disease provides a more accurate assessment of the metabolic status of these patients compared to standard evaluation of glycemic control respectively glycated hemoglobin. For this purpose I had the following objectives:

1. Evaluation of glycemic variability in patients with type 2 diabetes and chronic kidney disease stages 3-4.

2. Evaluation of glycemic variability in patients with type 2 diabetes and chronic kidney disease stage 5 ongoing continuous ambulatory peritoneal dialysis or hemodialysis.

3. Comparative analysis of glycemic variability in the three groups of patients.

I.2.2.Patients groups

The current study is a cross-sectional study that included 85 patients, conducted in the Emergency County Hospital Craiova during May 2011-May 2013.

The 85 patients were divided according to the presence of diabetes mellitus and chronic kidney disease into the following groups:

Group 1 - 25 patients with stage 3-4 chronic kidney disease and type 2 diabetes.

Group 2 - 20 patients stage 5 chronic kidney disease treated with CAPD including 11 patients with type 2 diabetes and 9 patients without type 2 diabetes.

Group 3 - 20 patients with chronic kidney disease stage 5 on hemodialysis including 10 patients with type 2 DM and 10 uremic hemodialysis patients without type 2 diabetes.

Group 4 - 20 patients without renal impairment, diabetes mellitus type 2. Normal renal function was defined as eGFR> 60 ml/min/1, 73 m2 and lack of albuminuria in two consecutive measurements every 3 months.

All patients included in the study was mounted for a period of 72 hours continuous glucose monitoring system with a prior training in the protection and calibration sensor device inserted.

The patients were instructed to calibrate the device which had to be done at least 4 times per day every 6 hours.

The calibration of the device was performed using capillary blood glucose self-determination with glucose meter One Touch Select Johnson & John.

I.2.3.Study parameters

The following parameters were studied:

- Demographic and anthropometric data: age, sex, body mass index (BMI)
- Glycosylated hemoglobin (HbA1c)
- Albuminuria
- Urea
- Creatinine
- Capillary blood glucose
- Glycemic variability indices evaluated on recordings by using the CGMS GlyCulator:

 mean interstitial glucose (mg / dl) – **MIG**

 percentage of time with glucose values greater than 180 mg / dl (**%> 180mg/dl**) or less than 70 mg / dl (**% <70mg/dl**)

 Mean amplitude of glycemic excursions (mg / dl) - **MAGE** - calculated based on the average differences between the highest and the lowest level of glucose only differences greater than the standard deviation (SD). MAGE provides a measure of glycemic variability within the same day with high amplitude and low frequency

 M100 index calculated as [1000 x [log10 (glucose/100)] 3] reported that glucose stability cuntifică the glucose values of 100mg/dl

 percentage coefficient of variation - **% CV** - calculated as the ratio between standard deviation and average glucose

 Fractal dimension - **FD** - based on Higuchi algorithm describes glucose variability with low amplitude and high frequency

 Mean of daily differences - **MODD** - calculated as the average absolute difference between glucose values corresponding time points in two consecutive days. MODD thus allows estimation of glycemic variability between two consecutive days

 Continuous overall net glycemic action - **CONGA** - 1, 2, 4 and 6 hours - glycemic variability within a predetermined time window.

I.2.4. Study of glycemic variability in patients with CKD stages 3-4

We included 45 patients (25 patients with diabetes and CKD 6M/19F, 67.5 ± 9.2 years and 20 diabetic patients without CKD 10M/10F, 57.5 ± 9.0 years) who CGMS mounted on a period of 72 hours.

HbA1c was higher in patients with diabetes and CKD compared with diabetic patients without renal impairment but the differences did not reach statistical significance.

Mean interstitial glucose was significantly higher in patients with diabetes and CKD compared with diabetic patients without CKD.

Also patients with diabetes and chronic kidney disease have had percentage of time glucose values greater than 180 mg / dl significantly higher than in diabetic patients without chronic kidney disease.

Percentage of time with glucose values below 70 mg / dl was higher in patients with type 2 diabetes compared with diabetic patients without CKD but the differences were not statistically significant.

Diabetic patients with CKD have had %C V, MAGE and M100 higher than diabetic patients without renal impairment but only for M100 MAGE differences were statistically significant.

All these results showed that patient with CKD and diabetes had a glycemic variability within the same day greater than diabetic patients without renal impairment.

Glycemic variability between two consecutive days (measured by MODD) was also significantly higher in patients with diabetes and CKD stages 3-4 compared with diabetic patients without CKD.

Diabetic patients with chronic kidney disease presented both in the same day glycemic variability (MAGE) and glycemic variability between two consecutive different days (MODD) higher compared with diabetic patients without chronic kidney disease.

Conclusions

Patients with chronic kidney disease and type 2 diabetes showed a significant metabolic imbalance and significant glycemic variability compared with diabetic patients without chronic kidney disease.

This study points out that HbA1c is not sufficient to accurately assess glycemic control, glycemic variability parameters using the CGMS recordings bringing a greater accuracy.

I.2.5.Study of glycemic variability in patients with CKD stage 5 ongoing continuous ambulatory peritoneal dialysis

We studied 32 patients which 20 peritoneal dialysis patients (11 patients with type 2 diabetes, 3M/8F, 65.8 ± 10.2 years, 9 patients without DM, 4M/5F, 60.2 ± 8.3 years) and 12 patients with type 2 diabetes without renal impairment (5M/7F, 54.6 ± 6.2 years).

All peritoneal dialysis patients had Kt / V> 1.7 and was performed in all patients prior to enrollment peritoneal equilibration test (PET), the results were processed using the program Adequest Baxter PD.

CGMS was performed in all patients for a period of 72 hours.

Paradoxically, peritoneal dialysis diabetic patients showed a lower HbA1c compared with diabetic patients without renal impairment but the results were not statistically significant.

Peritoneal dialysis diabetic patients had a significantly higher mean interstitial glucose compared with diabetic patients without renal dysfunction (p = 0,27).

The percentage of time glucose values greater than 180 mg / dl was also higher in peritoneal dialysis patients with diabetes compared with patients with diabetes without renal impairment and peritoneal dialysis patients without diabetes but the differences did not reach statistical significance.

The presence of blood glucose values over 180 mg / dl (2.8 ± 1.9) in peritoneal dialysis patients without diabetes indicate that the absorption of glucose from the peritoneum is responsible for short periods of sustained hyperglycemia in these patients.

Peritoneal dialysis diabetic patients had MODD and MAGE higher compared with diabetic patients without renal impairment but only MODD reached statistical significance which shows a glycemic variability between two consecutive days more pronounced in these patients.

Regarding the glycemic variability within a predetermined time window (CONGA) although values were markedly different for peritoneal dialysis diabetic patients, however, the differences were not statistically significant for any period of time.

The percentage of time that patients presented blood glucose <70mg/dl was higher in diabetic patients on dialysis indicating that peritoneal dialysis protects patients with and without diabetes mellitus against hypoglycaemia.

Although not all parameters in the same day glycemic variability differed significantly between diabetic patients with and without peritoneal dialysis it can be said that peritoneal dialysis determine the glycemic variability higher compared to nonPD diabetic patients especially glycemic variability between two consecutive days.

No glycemic variability parameter was significantly influenced by the status of the peritoneal membrane.

Conclusions

The current study provides evidence that the assessment of glycemic variability using CGMS records is more useful than HbA1c in quantifying metabolic imbalances in diabetic patients on peritoneal dialysis.

Results of the study highlighted that peritoneal dialysis induces glycemic variability between days and poor glycemic control, thus being a potential risk factor for progression of chronic complications of diabetes.

Status of the membrane and dialitic regimen does not influence glycemic variability in peritoneal dialysis patients.

I.2.6.Study of glycemic variability in patients with CKD stage 5 on hemodialysis

We studied 32 patients of which 20 hemodialysis patients (10 patients with type 2 diabetes, 5M/5F, 58.5 ± 8.2 years, 10 patients without diabetes, 4M/6F, 38.5 ± 9.9 years) and 12 patients with type 2 diabetes without renal impairment (5M/7F, 52.5 ± 7.3 years).

Comparative analysis of glycemic variability parameters pointed out that mean interstitial glucose on the day without dialysis in diabetic patients was higher than in both not dialysis diabetic patients and non-diabetic hemodialysis patients both days.

The percentage of time with glucose values> 180 mg / dl was higher on the day without hemodialysis in diabetic patients compared with diabetic patients not undergoing dialysis and hemodialysis patients without diabetes.

Analyzing the same day glycemic variability, quantified by MAGE has been shown it was higher in diabetic patients on hemodialysis both on the day of hemodialysis and on the day without dialysis compared with the other two groups of patients indicating that glycemic variability in the same day is influenced by the method of renal replacement therapy

Study glycemic variability between two consecutive days revealed by MODD showed that its value was significantly higher in diabetic patients undergoing hemodialysis compared with non dialysis diabetic patients.

M100 was higher in both the first day and the second day in non dialysis diabetic patients compared with hemodialysis patients with and without diabetes, but the differences were not statistically significant.

Comparing the values of CONGA 1h, 2h, 4h, 6h in the day without dialysis in diabetic patients undergoing hemodialysis to the values of the day equivalent to the other two groups the differences were not statistically significant .

Comparing the parameters of glycemic variability in diabetic patients undergoing hemodialysis between days with and without hemodialysis we obtained the following results: mean interstitial glucose ($p = 0.048$), % of time with glucose values> 180mg/dl and fractal dimension were higher in the day without hemodialysis.

Conclusions

Diabetic patients on hemodialysis presented on the day with hemodialysis a higher glycemic variability than the day without dialysis.

Glycated hemoglobin is not sufficient to assess glycemic variability in patients on hemodialysis.

I.2.7.Comparative analysis of parameters of glycemic variability in patients with CKD in predialysis and peritoneal dialysis vs hemodialysis

We included 36 patients with type 2 diabetes (15 patients with CKD stages 3-4 7M/8F, 66.8 ± 7.8 years, 10 patients with CKD stage 5 on hemodialysis, 5M/5F, 58.50 ± 8.2 years and 11 patients with CKD stage 5 ongoing continuous ambulatory peritoneal dialysis, 3M/8F, 65.8 ± 10.2 years).

Mean interstitial glucose was significantly higher in diabetic patients with chronic kidney disease compared with diabetic patients undergoing hemodialysis and peritoneal dialysis diabetic patients compared with hemodialysis diabetic patients.

Percentage of time with glucose values> 180 mg / dl, in the second day were significantly higher in predialysis patients compared with peritoneal dialysis diabetic patients. Also MODD was significantly higher in predialysis diabetic patients compared with peritoneal dialysis diabetic patients.

Conclusions

In summary it can be said that patients with diabetes and peritoneal dialysis have a glycemic variability within the same day higher than the diabetic patients undergoing hemodialysis but the latter have a higher glycemic variability between two consecutive days.

I.2.8. Predictors of glycemic control in patients with type 2 diabetes and CKD stages 3-5

The univariate analysis shows that predictors for metabolic imbalance, measured by HbA1c> 6.5% were interstitial glucose mean, percentage of time with glucose values> 180 mg / dl, M100 and MODD.

Multiple linear regression pointed out that just the percentage of time with glucose values> 180 mg / dl is the only independent predictor of metabolic imbalance measured by HbA1c> 6.5%.

II. Final conclusions

1. CGMS is a useful tool to more accurately assess of glycemic variability in patients with type 2 diabetes and CKD compared with glycated hemoglobin and capillary blood glucose self-monitoring, future studies are needed to identify how this monitoring system can help improve metabolic control and therapeutic management of these patients.

2. Patients with type 2 diabetes and chronic kidney disease have a higher glycemic variability compared with diabetic patients without renal dysfunction regardless of the stage of chronic kidney disease.

3. Glycemic variability is influenced by the method of renal replacement therapy in patients with type 2 diabetes and CKD stage 5.

4. The only parameter of glycemic variability which is an independent predictor for glycemic imbalance measured by HbA1c > 6.5 % is the percentage of time with glucose values > 180mg/dl.