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PERITONEAL DIALYSIS – RISK FACTOR FOR GLYCEMIC VARIABILITY ASSESSED BY CONTINUOUS GLUCOSE MONITORING SYSTEM

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Abstract

Background and Aims. *Peritoneal dialysis (PD) is accompanied by a multitude of factors that influence glycemic variability, and HbA1c does not detect dynamic glucose changes. In this study we wanted to assess glycemic variability, using a 72-hour continuous glucose monitoring system (CGMS), in 31 patients stratified according to the presence of type 2 diabetes and PD.* ***Materials and Methods****. The study included 31 patients (11 type 2 diabetic PD patients, 9 non diabetic PD patients and 11 type 2 diabetic patients without PD). Glycemic variability was assessed on CGM readings by: Mean Amplitude of Glycemic Excursion (MAGE), Mean of Daily Differences (MODD), Fractal Dimensions (FD), Mean Interstitial Glucose (MIG), Area Under glycemia Curve (AUC), M100, % time with glucose >180/<70 mg/dl.* ***Results.*** *The PD diabetic patients presented AUC, MIG and inter-day glycemic variability (MODD) significantly higher than diabetic patients without PD. In PD patients, the type of dialysis fluid in the nocturnal exchange and peritoneal membrane status did not significantly influence glycemic variability.* ***Conclusions****. CGMS is more useful than HbA1c in quantifying the metabolic imbalance of PD patients. PD induces inter-day glycemic variability and poor glycemic control, thus being a potential risk factor for chronic complications progression in diabetic patients.*

key words: *diabetes mellitus type 2, medical devices, peritoneal dialysis*

Background and Aims

Peritoneal dialysis (PD) ranks third place in Europe and USA among therapies of renal function substitution (after hemodialysis and kidney transplantation). Thus, according to the European Renal Association – European Dialysis and Transplant Association (ERA - EDTA) registry, in the year 2009, 51% of patients with end stage renal disease (ESRD) were undergoing hemodialysis, 41% were kidney transplanted and 7% were treated with PD [1]. United States Renal Data System 2011 Annual Data Report indicated that in USA 65% of the ESRD patients underwent hemodialysis, 30% received a kidney transplant and 5% performed PD [2]. In Romania, PD represents the second method of renal replacement therapy for ESRD patients after hemodialysis. In 2011, the Romanian Renal Registry reported that PD

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was initiated in 5.8% of ESRD patients, this percent being similar to that reported at worldwide level [1].

Diabetes mellitus (DM) represents currently the leading cause for ESRD. In Romania, with 14.8% of ESRD patients, DM constitutes the primary cause of kidney failure [1]. The diabetic PD patients have a high incidence of complications and comorbidities, thus requiring special management strategies. Glycemic control in PD patients with DM is very difficult to be achieved mainly due to the uremic status of these patients and to glucose exposure from peritoneal dialysate [3]. Sustained chronic hyperglycemia and acute glucose fluctuations constitute the main features of metabolic impairment in PD DM patients.

Glycemic variability seems to have more deleterious cardiovascular effects compared to sustained hyperglycemia, especially due to oxidative stress activation. This association is supported by the strongly positive correlation between the urinary excretion rate of isoprostane 8-iso-prostaglandin-F2α (oxidative stress marker) and glycemic variability [4,5].

Even though there is still no “gold standard” method for glycemic variability assessment, the measurement of several indices using Continuous Glucose Monitoring (CGM) readings may be an useful tool that allows efficient discrimination between sustained chronic hyperglycemia and acute glucose fluctuations [4-6].

Several studies indicated that in PD patients insulin resistance and glucose overload may represent important factors that significantly influence glycemic variability [7]. The glucose excursions are exacerbated and difficult to assess due to the influence of both the uremic status and PD *per se* [8].

Although glycated hemoglobin (HbA1c) is considered a standard parameter of glycemic control, according to the Kidney Disease Improving Global Outcomes (KDIGO), in ESRD patients this may be falsely low (due to the reduced erythrocytes life span, hemolysis, iron deficiency, etc.), but also falsely high due to hemoglobin carbamylation and acidosis [9].

Taking into account the multitude of factors influencing the glycemic control in PD patients, as well as the fact that HbA1c and self-monitored blood glucose do not detect the entire dynamic glucose changes, we hypothesize that the assessment of glycemic variability using CGMS data may provide a more accurate evaluation of the metabolic status in these patients. In order to test this hypothesis, we attempted to assess comparatively glycemic variability (estimated using 72-hour CGMS) in 31 subjects stratified according to the presence of PD therapy and diabetes. We also intended to evaluate the influence of glucose daily load (GDL) and of peritoneal transport status on glycemic variability in subjects undergoing PD therapy.

Material and method

Subjects

We performed a cross-sectional study on 31 patients, stratified in 3 groups: 11 PD diabetic patients (PD+DM+), 9 PD non-diabetic patients (PD+DM-) and 11 diabetic patients without PD (PD-DM+).

Inclusion criteria were: signing of the informed consent for participation in the study and maintenance of PD for at least 3 months. Exclusion criteria were: chronic consumptive diseases (hepatitis, neoplasia, hematological diseases, tuberculosis, HIV, etc), acute infections or peritonitis at the date of enrolment, mental illnesses, pregnancy and lactation.

The PD patients consecutively presented at routinely visits in our clinical department. All PD patients were adequately dialyzed: kt/v> 1.7

and a peritoneal equilibrium test (PET) was performed, the results being processed with the Adequest Baxter PD Program [10].

Type 2 diabetic non PD patients, sex and age matched, which regularly attending the Diabetes Ambulatory were invited to participate in this study as a control group.

All subjects signed an Inform Consent prior to study admission. The study was approved by the local Ethics Committee and performed according to the Helsinki declaration and good clinical practice guidelines.

Study protocol

The CGMS sensor (DexCom SEVENPLUS) was subcutaneously inserted in all subjects included in the study and maintained for 72 hours, allowing interstitial glucose measurements every 5 minutes. The CGMS calibration was performed by recording at least 4 capillary blood glucose values with a glucose meter which does not interfere with Icodextrin from the dialysis fluid. All the subjects had the same daily caloric intake.

The PD patients had two different dialytic treatment regimens: 4 exchanges with 2L 1.36% glucose (13 patients), 3 exchanges with 2L 1.36 % glucose and a night long dwell with Icodextrin (7 patients).

The following data were recorded: demographic characteristics, medical history (type 2 DM and PD duration, current therapy), anthropometric parameters, GDL (entire amount of glucose introduced in peritoneal cavity during dialysis exchanges), peritoneal transport status (assessment of peritoneal membrane transport function using PD Adequest program). HbA1c was measured in all subjects. The following glycemic control and variability indices were assessed on CGM readings, using the GlyCulator application [11,12]:

- Mean level of 24 h interstitial glucose value (MIG)
- Area under glycemia curve (AUC) of glycemic course within the range of CGMS (40-400 mg/dl), using trapezoidal method [7]. AUC was expressed in mg.1440 $min^{-1}.dl^{-1}$. M100 index calculated as $[1000 \times [\log_{10}(glucose/100)]^3]$ which quantifies the stability of glycemia reported to the 100 mg/dl glucose value [13].
- Percentage of time with glucose values above 180 mg/dl (%>180mg/dL) and bellow 70 mg/dl (%<70mg/dL).
- Mean amplitude of glycemic excursions (MAGE) calculated based on the mean of differences between consecutive glucose values picks and nadirs, only for differences greater than the SD. MAGE provides a measure of intra-day, high amplitude, glucose variability [13].
- Fractal dimensions (FD) calculated using the Higuchi algorithm. FD describes glucose variability of small amplitude and high frequency [14,15].
- Mean of daily differences (MODD) calculated as the mean of absolute differences between glucose values at corresponding time points of consecutive days. MODD allows the estimation of inter-day glucose variability [16].

Statistical analysis

Continuous variables are expressed as means ± standard deviation; categorical variables are expressed as percentages. The variables were tested for normal distribution using the Kolmogorov-Smirnov test. Comparisons between different groups were performed using parametric or nonparametric tests, depending on the variables distribution. Values of $p < 0.05$ were considered significant. SPSS19.0 software was used for analysis.

Results

All 31 patients fulfilling the inclusion criteria had satisfactory CGMS recordings for 72 hours. The demographic, clinical and biological characteristics of the subjects are summarized in Table 1.

Table 1. Comparative evaluation of clinical and biological parameters between groups.

Variables	**PD+DM+ (n=11)**	**PD+DM- (n=9)**	**PD-DM+ (n=11)**
Sex (M/F)	3/8	4/5	5/6
Age (years)	65.8±10.2	60.2±8.3	57.6±9.5
BMI (kg/m^2)	28.8±5.1	28.6±4.6	27.9±1.8
PD duration (years)	4.2±2.2	4.4±1.9	-
PET (L, LA / H, HA)	3/8	2/7	-
GDL (g/day)	104.7±16.4	99±17.2	-
Type 2 DM duration (years)	7.9±4.7	-	8.1±5.7
OAD/Insulin (no. of subjects)	1/10	-	2/9

L - low transporters; LA - low average transporters; H - high transporters; HA - high average transporters; OAD - oral anitidiabetic drugs; There were no significant differences between the groups for all variables.

Table 2. Analysis of glycemic parameters according to PD and T2DM presence.

Variables	PD+DM+ (n=11)	PD+DM- (n=9)	PD-DM+ (n=11)
HbA1c (%)	6.9±1.6%**	5.6±0.2***	6.7±1.2
AUC (mg.1440 min^{-1}.dl^{-1})	233281±22169*,**	169716±198852	199696±59989
MIG (mg/dl)	162.6±15.5*,**	118.2±13.8	139.2±41.8
M100	15.5±8.3**	1.9±1.2	16.3±11.9
%>180mg/dl	26±12.9**	2.8±1.9	20.9±11.17
%<70mg/dl	0.9±0.2	3.9±1.3	2±1.8
MAGE (mg/dl)	116.6±54.1**	57.7±16.3	80.8±50.1
FD	1.2±0.06	1.3±0.09	1.3±0.06
MODD (mg/dl)	35.2±14.5*,**	18.1±3.5	19.8±7.7

*p<0.05:PD+DM+vsPD-DM+; **p<0.05:PD+DM+vsPD+DM-; ***p<0.05:PD+DM-vsPD-DM+

Analysis of glycemic variability according to PD and type 2 DM presence

PD diabetic patients had an AUC and mean of interstitial glucose and inter-day glycemic variability (quantified by MODD) significantly higher compared to diabetic patients without PD (Table 2, Figure 1, Figure 2). Although MAGE was also higher in PD diabetic patients compared to those without PD, the difference did not reach a statistical significance (Table 2, Figure 1).

As expected, diabetic PD patients had significantly higher HbA1c, AUC, mean interstitial glucose values, inter-day and high amplitude/low frequency intra-day glycemic variability compared to non diabetic PD patients (Table 2, Figure 1, Figure 2).

Influence of peritoneal dialysis fluid type used in nocturnal exchange and peritoneal transport status on glycemic variability

Analyzing glycemic variability during the night dialysis exchange (10.00 PM to 8.00 AM time interval) we noticed that the subjects with

Icodextrine, compared to those with glucose solution, did not exhibits significantly different glycemic variability (Table 3). MODD was higher (but without statistical significance) in the subjects with glucose in long dwell, compared to the subjects with Icodextrine, thus indicating the influence of the variable peritoneal glucose absorption on the inter-day glycemic variability. The peritoneal membrane status did not significantly influence glycemic variability (Table 3).

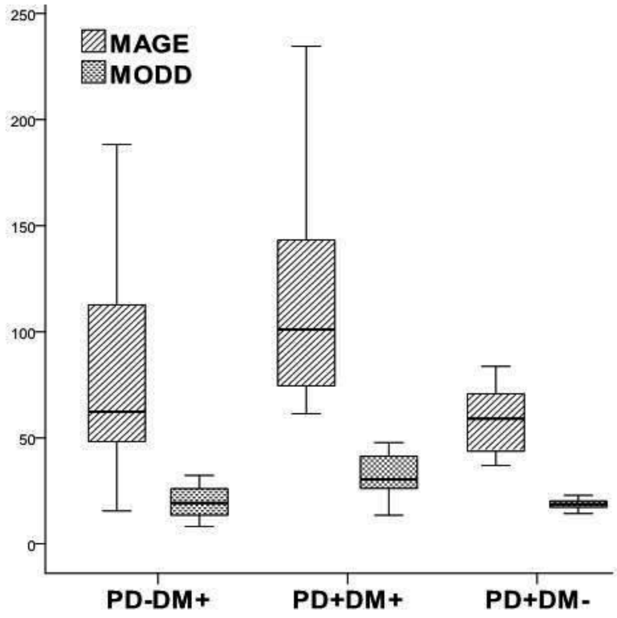

Figure 1. *Box Plot indicating the distribution of MAGE and MODD, according to PD and T2DM presence*.

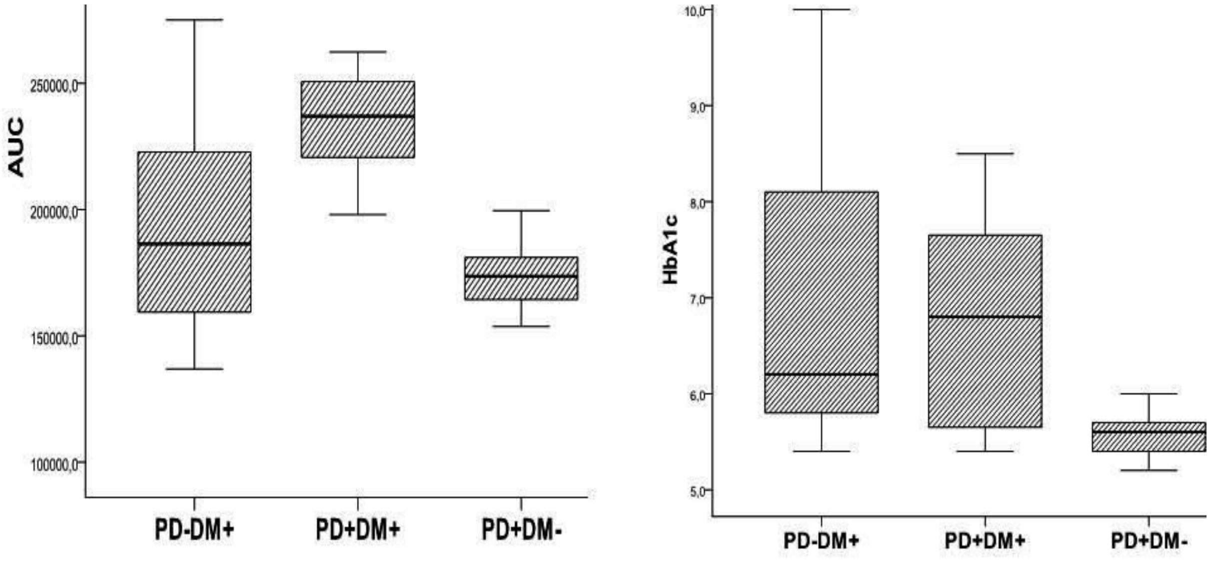

Figure 2. *Box Plot indicating the distribution of AUC (left), HbA1c (right), according to PD and T2DM presence*.

Discussions

The results of our study indicate that diabetic patients undergoing peritoneal dialysis had higher inter-day (MODD) and more pronounced glycemic imbalance revealed by high glucose AUC and MIG, compared to diabetic subjects without PD.

Table 3. Analysis of glycemic variability according to the type of peritoneal dialysis fluid in the night exchange and to the peritoneal membrane status.

Variables	Peritoneal membrane status		Type of dialysis fluid in the night exchange	
	LA+L (n=5)	H+HA (n=15)	Glucose (n=13)	Icodextrin (n=7)
HbA1c (%)	6.1±1	6.3±1.3	6.2±1	6.2±1.2
AUC (mg.1440 min^{-1}.dl^{-1})	202130±31430	205526±41466	210694±31767	193503±49351
MIG (mg/dl)	140.8±21.8	143.2±28.9	146.8±22.1	134.6±34.4
M100	135.8±20.7	138.3±26.5	9.3±7.4	9.3±7.6
%>180mg/dl	13.4±10.7	15.7±11.5	16±13.5	13.5±9.9
%<70mg/dl	0.6±0.3	0.8±0.4	0.28±0.2	1.6±0.4
MAGE (mg/dl)	90.8±51.7	89.8±52	89.1±43	91.9±66.2
FD	1.2±0.05	1.2±0.08	1.2±0.06	1.3±0.01
MODD (mg/dl)	29.7±10.9	26.7±15	28.7±14.4	25.2±13.5

There were no significant differences between the groups for all variables; All variables, except HbA1c, were quantified in the 10.00 PM - 8.00 AM time interval

The exposure to glucose from the peritoneal dialysis fluid and its variable peritoneal absorption represent potential factors responsible for the glycemic variability in the PD subjects.

Previous studies have indicated that 70% of glucose from the dialysis fluid is absorbed through the peritoneum, leading to hyperglycemia and glycemic variability [17,18]. Several studies have shown that dialysis fluid with 1.5% glucose concentration induced only a slight increase of glycemia [19].

Lack of reproducibility of glucose peritoneal absorption secondary to the peritoneal infectious inflammatory diseases might explain the glycemic variability in PD subjects. Inter-day glycemic variability in diabetic PD patients may be a consequence of variable absorption of glucose from the peritoneum secondary to diabetic and uremic neuropathy.

Although HbA1c in diabetic PD patients was higher compared to the diabetic non PD patients, the differences did not reach statistical significance, indicating a minor influence of glucose from the dialysis fluid.

Regarding the type of dialysis fluid from the night exchange, there were no significant difference of glycemic variability between the patients which use 1.36% glucose solutions and those with icodextrine. Various studies reported a significant increase of interstitial glucose levels, but only in the PD subjects, who used 3.86% or 2.5% glucose solutions during the night peritoneal exchange [20-22]. In contrast with other studies that analyzed the influence of Icodextrin on the overall glycemic control, our study analyzed the glycemic variability also during the night exchange when Icodextrine or glucose were used. There are contradictory data regarding the influence of Icodextrin on the HbA1c levels. Similar to Gradden et al and Hithaishi et al, we showed that Icodextrin in the night exchange did not influence HbA1c levels in diabetic patients [23,24]. However, other recent studies reported a positive influence of Icodextrin on the metabolic control [19-22].

Finally, we found that peritoneal transport status did not determine any significant differences of glycemic variability, results concordant with those of other studies [17].

This proof-of-principle study has limitations due to the small sample size. However, the results from this sample date are strongly suggestive that a larger study on the glycemic variability in diabetic PD patients is needed.

Conclusions

The current study provided evidence that the assessment of glycemic variability using CGMS recordings is more useful than HbA1c in quantifying the metabolic imbalance in diabetic patients with peritoneal dialysis. Our findings emphasized that peritoneal dialysis induces inter-day glycemic variability and poor glycemic control, thus being a potential risk factor for the progression of diabetic chronic complications.

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