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Disparity of Interstitial Glucose for Capillary Glucose in Dialysis Diabetic Patients

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1. Abstract

The prevalence of chronic kidney disease (CKD) has steadily increased and diabetes is now considered the leading cause of end-stage kidney disease (ESRD). Glycemic control in chronic renal patients on dialysis presents additional difficulties because both uremia and dialysis can affect insulin secretion and tissue insulin sensitivity. In dialysis patients, blood glucose measurement may be affected as hemodialysis causes rapid and marked changes in body fluid volume, including subcutaneous and interstitial tissue. Continuous glucose monitoring is a critical clinical tool for the treatment and management of diabetes. However, experience with CGM in patients with CKD and dialysis is limited in clinical practice. The objective was to compare the disparities in blood glucose measurements between the capillary measurement and the interstitial measurement in diabetic patients on dialysis. We carried out a 2-week randomized prospective study with 12 patients for glycemic monitoring by fingerstick associated with an interstitial measurement sensor.

Results: In the comparison of pre-dialysis measurements of capillary and interstitial blood glucose, no disparities were observed, in relation to visit 0, in the median and mean in visits 1

(p=0.112 and p=0.291 respectively), 2 (p=0.729 and p =0.764 re- spectively) and 5 (p=0.285 and p=0.151 respectively). Statistical inequality was observed in terms of median and mean at visits 3 (p=0.028 and p=0.049 respectively) and 4 (p=0.033 and p=0.031 respectively). In the comparison of post-dialysis capillary meas- urement, no statistical differences were observed in any visits of the median or mean (V1 p=0.544 and p=0.436, V2 p=0.686 and p=0.298, V3 p=0.174 and p=0.153, V4 p=0.272 ep=0.214 and V5
p=0.225 and p=0.368 respectively). The means of absolute relative differences (MARDs) calculated from the measurement of capillary blood glucose as a reference when compared to the first hemodialysis session by the sensor showed statistical differences only in the last session (p = 0.037). The overall MARD value was21.4% (± 17.8)

Conclusion: The disparity in the measurement of interstitial and capillary blood glucose increases over the days of use. There is a greater divergence of measurement at the end compared to the beginning of each dialysis session.

2. Introduction

Technological developments have provided significant advances in the diagnosis, monitoring and treatment of DM2. Yet patients

remain with increased mortality and morbidity compared to the general population. More than half of affected patients are unable to obtain and maintain glycated hemoglobin (HbA1c) levels in the glycemic target <7% after 3 years despite drug treatment [1]. The United Kingdom Prospective Diabetes Study (UKPDS) established a strong association between observed levels of HbA1c and the risk of macrovascular and microvascular complications. In that study, a 1% reduction in HbA1c was associated with a 14% decreased risk for acute myocardial infarction (AMI) and a 37% reduction in microvascular complications [2]. Intensive diabetes management reduces the risk of micro and macrovascular complications, but at the same time increases the risk of hypoglycemia. Diabetic nephropathy is one of the costliest complications for the health system because patients with this condition often progress to dialysis, an expensive treatment that makes it difficult for the patient to enter the labor market. American data showed that expenditures on dialysis CKD exceeded US$ 120 billion in 2017. As an aggravating factor, cardiovascular mortality increases in proportion to the decrease in glomerular function, and diabetics who start dialysis treatment, less than 20% survive after 5 years [3]. Among hemodialysis patients, mortality is higher in those with diabetes, therefore, glycemic control is of fundamental importance for the prevention of CKD [4]. Despite increasing medical care regarding the emergence of complications from diabetes, end-stage renal disease was the only one that did not show a decline in incidence [5]. Glycemic control of chronic kidney patients on dialysis presents additional difficulties because both uremia and dialysis can affect insulin secretion and tissue insulin sensitivity. In these patients, there is an increase in insulin resistance, increased gluconeogenesis Devices that perform interstitial continuous glucose monitoring (CGM) provide a means to facilitate diabetes control, resulting in better HbA1c levels, less glucose variability, less frequent hypoglycemic episodes, better quality of life, and more lifestyle flexibility. Robust clinical trials have demonstrated the benefit for controlling type 1 [6] and type 2 [7] diabetes. In these studies, there was a significant reduction in time in hypoglycemia below 70 mg/dL and below 54 mg/dL in DM1 and DM2, respectively, in addition to reducing the frequency of hypoglycemic events. The transcutaneous interstitial CGM can also indicate a rate at which the glucose is changing and alert the user to any hypoglycemia or hyperglycemia. Several clinical trials have measured HbA1c levels in CGM patients, with HbA1c reduction ranging from 0.4 to 0.6% in diabetic patients and reduction in hypoglycemic episodes in patients with glucose sensors using them by at least 70% of time [8].

Despite the benefits, the use of CGM sensors is still very limited, whether due to the cost, non-refund by health care providers, medical inertia, or the small number of studies attesting to the accuracy in specific situations, such as in patients undergoing dialysis treatment. In these patients, the use of CGM emerges as a promising tool for the assessment of glycemic control, allowing the tracking of the physiological glucose dynamics in greater detail, both in relation to meals and hemodialysis sessions [9]. The Libre Flash sensor is a 3-electrode enzymatic system. When glucose molecules diffuse from interstitial tissue across the outer membrane to the matrix, they are oxidized by the enzyme glucose oxidase. The resulting electrons are transferred from the enzyme to the mediating molecules and then transported to the electrode using neighboring mediator molecules. The measurement signal is an electrical current, which current is proportional to the concentration of glucose at the measurement site [10]. In dialysis patients, blood glucose measurement may be affected as hemodialysis causes rapid and marked changes in body fluid volume, including subcutaneous and interstitial tissue. The experience with CGM in patients with CKD and dialysis is limited both in research and clinical settings [11]. There are currently no studies on the differences in capillary and interstitial glycemic measurements in diabetic dialysis patients.

2. Subjects and Methods

Study Design

2-week randomized prospective exploratory study. Carried out at the Davita Meireles Dialysis Clinic / Diabetes Research Center. All study methods were performed in accordance with relevant guidelines and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan and under the Code of Ethics of the Declaration of Helsinki, 1964, and written informed consent was obtained from all the participants. Thirteen patients were evaluated for initial screening. One patient after sensor placement was discontinued for having been transplanted before the end of follow-up. Eligibility criteria included type 2 diabetics with diagnosis time greater than 4 months, in dialysis therapy for at least 30 days.

The study consisted of a period of two weeks, of intensive monitoring period with CGM Libre flash and digital capillary blood glucose. In the first dialysis session, the CGM Libre Flash sensor was placed in the upper-posterior part of the arm contralateral to the arteriovenous fistula 60 minutes before the beginning of the dialysis session.

Capillary and interstitial blood glucose were simultaneously measured and compared both at the beginning of each dialysis session (pre-dialysis measure) and at the end (post-dialysis measure). To gauge capillary blood glucose levels as a reference, all participants used the Accu-Chek Guide. Data from the FreeStyle Libre reader was downloaded using the FreeStyle Libre software program, version 1.0 (Abbott Diabetes Care) and saved in log files as text data.

Statistical Analysis

In order to characterize the population of each, descriptive analysis of frequency measurements was performed when the variable was qualitative; and mean and its variations when the variable was quantitative. Quantitative variables were tested for normality using

the Shapiro-Wilk test. For the independent variables, in the presence of normality, the homogeneity of the variance of the groups was evaluated using the Levene`s test. Given the homogeneity, the difference was tested using an independent t-test. In case homogeneity was not proven by the Levene`s test, the differences between the independent variables were calculated using the Welch test. The distinction between quantitative variables without normality was verified by the Mann-Whitney test. The Mean Absolute Relative Difference (MARD) was used to assess the accuracy of the Freestyle Libre interstitial sensor. The MARD of each hemodialysis session was compared with that of session 0.

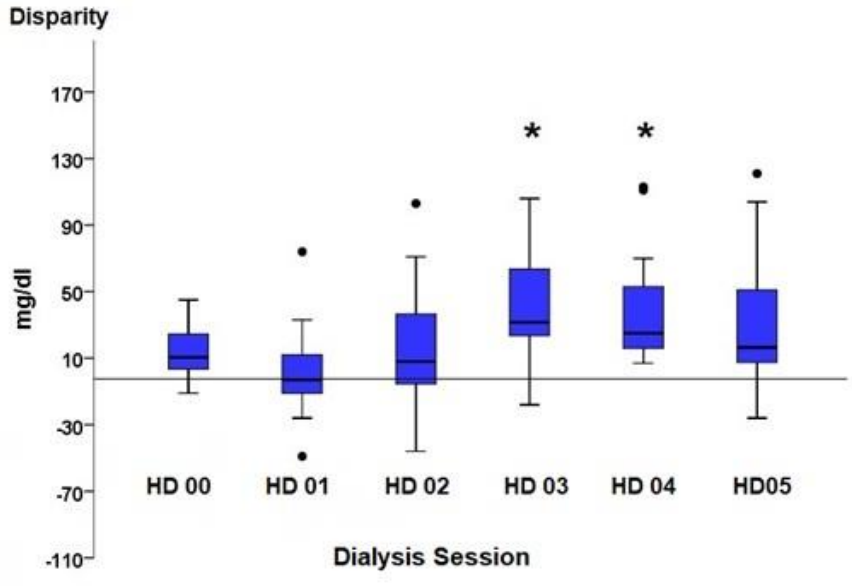
3. Results

The study enrolled 12 patients to initiate CGM Libre Flash monitoring simultaneously with an Accu-Chek Guide glucometer. The baseline characteristics are described in (Table 1). When comparing pre-dialysis measurements of capillary and interstitial blood glucose, no disparities were observed, in relation to visit 0, in the median and mean in visits 1 (p=0.112 and p=0.291 respectively), 2 (p=0.729 and p=0.764 respectively) and 5 (p=0.285 and p=0.151 respectively). Statistical inequality was observed in terms of median and mean at visits 3 (p=0.028 and p=0.049 respectively) and 4 (p=0.033 and p=0.031 respectively). (Table 2 and Graph 1). In the comparison of post-dialysis capillary measurement disparity with the measurement by the interstitial sensor, no statistical differences were observed in any visits of the median or mean (V1 p=0.544 and p=0.436, V2 p=0.686 and p=0.298, V3 p=0.174 ep=0.153, V4 p=0.272 and p=0.214 and V5 p=0.225 and p=0.368 respectively) (Table 3 and Graphic 2). The mean relative absolute difference (MARD) was calculated using capillary blood glucose as a reference. A progressive increase in MARD from the first session during each measurement was observed, reaching a statistically significant peak in session 5 (p=0.037) (16.5 ± 15.2, 15.6 ± 12.6, 19.0 ± 15.8, 25.3 ± 17.5, 23.2 ± 18.8, 28.8 ± 23.2, from the first to the sixth session respectively). The overall MARD value was 21.4% (± 17.8) (Graphic 3). Pre-dialysis MARD was positively correlated with age, BMI, dialysis fluid loss, time on dialysis treatment and glycated hemoglobin. It showed a negative correlation with hemoglobin. Regarding post-dialysis MARD, it showed a positive correlation with age, BMI and glycated hemoglobin. And a negative relationship with dialysis fluid loss, time on dialysis treatment and glycated hemoglobin, the latter being the only one with a statistically significant correlation (p=0.032) (Table 4).

Table 1: Clinical and Laboratory Data

	Glicemia intersticial
Sex (M:F)	(8:4)
Age (years)	66.8 ± 8.0
Time in dialysis treatment (years)	4.7 ± 3.4
BMI with dry weight in V-3 (kg/m2)	25.5 ± 2.7
Loss volume per session (liters)	2.0 ± 0.5
Hematocrit (%)	36.7 ± 7.3
Hemoglobin (g/dl)	11.9 ± 2.2
Hypoglycemia episodes in the first week	0

Data presented as mean with standard deviation.



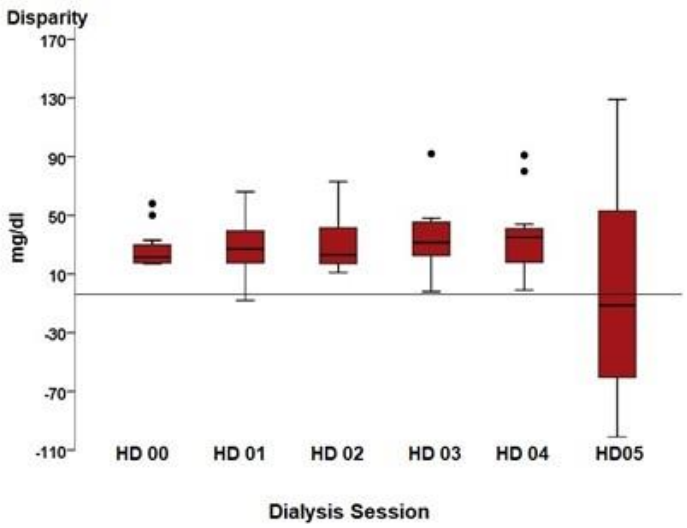
V0)

Graph 1: Disparity between capillary and interstitial blood glucose in pre-dialysis in mg/dl (* statistical difference in relation to the mean of the reference measure)

Table 2: Analysis of the Disparity of the Pre-Dialysis Blood Glucose Measurement Between Capillary and Interstitial Glucometers

		Percentiles of the disparity of pre-dialysis measurement of capillary to interstitial blood glucose				
	Quartile 25 mg/dl (%)	Quartile 50 mg/dl (%)	Quartile 75 mg/dl (%)	p of mean	Median mg/dl (%)	p of median
HD session 0	1.25 (-15.3)	10.50 (-7.0)	25.25 (-2.5)	_	13.2 ± 4.5 (7.9 ± 8.3)	_
HD session 1	-13.50 (-8.1)	-3.00 (18.5)	14.00 (57.2)	0.112	2.5 ± 8.8 (14.0 ± 17.3)	0.291
HD session 2	-7.25 (-16.5)	8.00 (-5.3)	42.25 (5.0)	0.729	17.0 ± 11.6 (9.7 ± 20.6)	0.764
HD session 3	21.25 (-27.9)	31.50 (-19.5)	76.75 (-11.3)	0.028	39.2 ± 11.2 (21.6 ± 19.8)	0.049
HD session 4	15.00 (-27.8)	25.00 (-15.1)	61.50 (-0.8)	0.033	40.8 ± 10.6 (21.6 ± 19.0)	0.031
HD session 5	6.75 (-28.9)	16.50 (-12.9)	52.00 (1.4)	0.285	33.4 ± 12.4 (15.9 ± 26.8)	0.151

Data presented in quartiles of mg/dl (percentage). Median in mg/dl (percentage). P significant when < 0.05

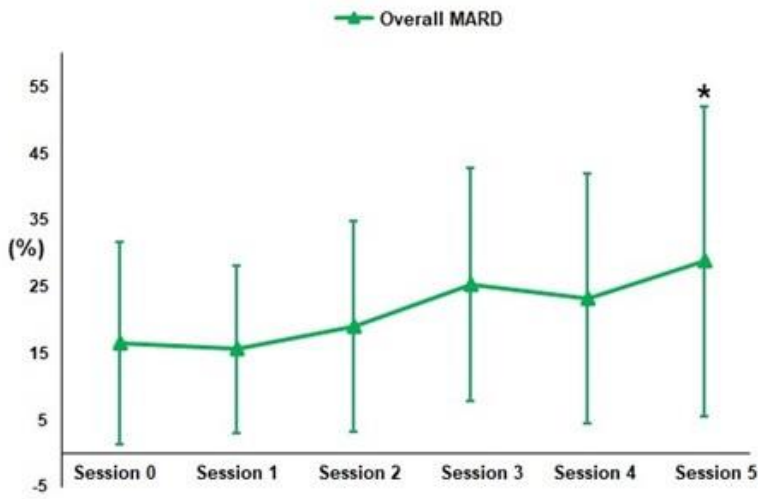


Graph 2: Disparity between capillary and interstitial blood glucose in post-dialysis in mg/dl (* statistical difference in relation to the mean of the reference measure)

Table 3: Analysis of the Disparity of the Post-Dialysis Blood Glucose Measurement Between Capillary and Interstitial Glucometers

		Percentiles of the disparity of post-dialysis measurement of capillary to interstitial blood glucose				
	Quartile 25 mg/dl (%)	Quartile 50 mg/dl (%)	Quartile 75 mg/dl (%)	p of mean	Median mg/dl (%)	p of median
HD session 0	17.25 (-21.1)	21.50 (-14.0)	31.50 (-11.0)	-	20.33 ± 8.56 (12.7 ± 27.8)	-
HD session 1	16.75 (-27.7)	27.00 (-19.1)	40.75 (-12.0)	0.544	28.50 ± 4.91 (-19.2 ± 12.8)	0.436
HD session 2	16.00 (-28.7)	26.00 (-16.2)	47.75 (-12.8)	0.686	31.67 ± 6.29 (-22.6 ± 14.8)	0.298
HD session 3	20.75 (-40.5)	31.50 (-22.3)	46.75 (-13.4)	0.174	39.83 ± 10.00 (-26.6 ± 19.14)	0.153
HD session 4	15.00 (-34.4)	35.00 (-21.1)	42.50 (-8.9)	0.272	35.25 ± 7.92 (-24.8 ± 19.3)	0.214
HD session 5	-62.75 (-47.5)	-11.50 (-20.4)	62.5 (-8.4)	0.225	-0.67 ± 20.94 (-27.7 ± 24.2)	0.368

Data presented in quartiles of mg/dl (percentage). Median in mg/dl (percentage). P significant when < 0.05



Graph 3: Overall MARD of each dialysis session (*statistical difference in relation to the reference measure V0)

Table 4: Correlation of MARD with Clinical Variables in Pre- and Post-Dialysis

Correlation of Mean Absolute Relative Difference (MARD) with clinical and laboratory variables				
	Pre-dialysis (r)	p	Post-dialysis (r)	p
Age	0.055	0.648	0.122	0.307
Body mass index	0.194	0.103	0.032	0.79
Water loss (Ultrafiltrate)	0.087	0.47	-0.152	0.202
Time on dialysis treatment	0.026	0.83	-0.169	0.156
Hemoglobin	-0.13	0.276	-0.02	0.867
Glycated hemoglobin	0.183	0.124	0.253	0.032

Data presented in mean absolute relative difference with standard deviation. P significant when < 0.05

4. Discussion

Numerous studies have demonstrated the benefits of glycemic management in patients with chronic kidney disease undergoing dialysis treatment. However, the literature lacks data that designate the ideal methodology to assess diabetes control. Glycated hemoglobin, frutosamina, and glycated albumin have limitations in chronic renal patients as they do not accurately reflect glucose variability or risk of hypoglycemia. CGM is becoming one of the main tools for glycemic control [12]. Some studies already reveal an improvement in the management of DM2 who are on hemodialysis with the CGM [13]. When evaluating the disparity between the capillary blood glucose meter reading with the Flash sensor monitor, our results indicate that in the pre-dialysis measurements of visits 3 and 4 there were significant reading distortions, both in relation to the median and to the mean readings. In V4, specifically, the mean was much higher than the median due to some outliers that may have distorted the sample. Interestingly, the median and mean of the disparities observed in post-dialysis readings were not statistically different despite the large variability of values at V5.

It is of fundamental importance that health professionals who deal with dialysis patients understand the differences between measurements with an interstitial sensor and measurements of capillary blood glucose, in order to promote therapeutic management to avoid exaggerated glycemic incursions or hypoglycemia resulting from the use of erroneous insulin doses.

The metric used to assess the clinical accuracy of a new glycemic measurement mechanism is the mean absolute relative difference (MARD). Low values suggest a high system accuracy. Our study showed MARD values different from the mean observed in studies with non-dialysis patients, but in agreement with those that evaluated only dialysis patients. This difference in MARDs can be explained, at least partially, as a result of the volume changes that patients experience during the dialysis session. Large changes in the plasma reflect directly on the interstitium, which can impair the sensor reading on the microfilament inserted into the subcutaneous tissue. In patients without dialysis chronic kidney disease, the MARD with the interstitial sensor demonstrated a stable pattern over the days that fluctuates, depending on the study, between 10% and 17.8% [14-16]. The reason for the progressive increase in MARD with the course of each dialysis session is not yet known, but we hypothesized the influence of the body's natural inflammatory response to sensor insertion, which has been shown to affect [12] the concentration of glucose in the interstitial fluid [17]. Our results did not show a statistically significant correlation of MARD with age, body mass index, fluid loss, time on dialysis or hemoglobin levels, in agreement with other data in the literature

[14,16]. As limitations of the study, we mention the sample size the lack of comparison with other markers of glycemic control in dialysis patients, such as frutosamina and glycosylated albumin, and finally, the lack of use in other sensor sites.

6. Conclusion

The reading disparity between the interstitial blood glucose sensor and the capillary blood glucose increases over the days in dialysis patients. There is a trend of increasing values in capillary blood glucose compared to interstitial glucose. MARD values in dialysis patients are higher than those in non-dialysis patients, and there is a progressive increase for each session. There is also a positive and statistically significant correlation between glycated hemoglobin values and MARD, demonstrating that the worse the control of diabetes, the worse the accuracy of the interstitial system.

7. Ethics Approval and Consent to Participate

The study protocol was approved by the local Ethical Committee (Comitê de Ética em Pesquisa envolvendo seres humanos (COMEPE) from Centro Universitário Christus - Unichristus) and all eligible candidates had to provide signed informed consent before enrolling in the study. The authors confirm that they have read and agreed to the full submission statement below, including that the submission is original and has not been previously published, all permissions have been obtained, the manuscript includes all the relevant statements and acknowledgements, the copyright is transferred to Diabetology & Metabolic Syndrome editors.

8. Consent for Publication

The authors confirm that they have read and agreed to the full submission statement below, including that the submission is original and has not been previously published, all permissions have been obtained, the manuscript includes all the relevant statements and acknowledgements, the copyright is transferred to Diabetology & Metabolic Syndrome editors.

9. Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

10. Funding

No source of funds was used to carry out this study.

11. Contributorship

Each author contributed individually and significantly to the development of this article. Hissa MRN: intellectual concept of the article, literature review, data collection and statistical analysis; Hissa MN: literature review, statistical analysis and review of the final article. Hissa PNG: literature review, statistical analysis and review of the final article. Guimarães SB: literature review, statistical analysis and review of the final article.

12. Conflict-of-Interest Disclosure

No competing interests from any author.

13. Acknowledgement

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