Revista Portuguesa de Diabetes. 2021; 16 (4): 164-170

The Stress Hyperglycemia Ratio as Predictor of Clinical Outcomes in Geriatric Patients

O Rácio de Hiperglicemia de Stresse como Preditor de Resultados Clínicos em Doentes Geriátricos

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Abstract

Purpose: Hyperglycemia is associated with higher morbidity and mortality rates in hospitalized patients. Stress hyperglycemia ratio (SHR) is a possible predictor of stress induced hyperglicemia. Older patients lack adequate severity risk indexes. We aimed to clarify the relationship between SHR and severity illness markers in geriatric patients with acute pyelonephritis (ANP) or community acquired pneumonia (CAP).
Methods: This is a retrospective study on patients older than 80 years. Clinical and laboratory data comprised systemic inflammatory response syndrome (SIRS) criteria, C-reactive protein (PCR) (mg/L); glomerular filtration rate (GFR) (mg/dL/1.73m^2); length of stay, in days; mortality rate. SHR was calculated. Patients were divided in groups – diabetic (DM) *versus* non-diabetic (NDM), and further separated according to their diagnosis into ANP and CAP groups. Statistical analysis was performed using SPSS software version 22,0.
Results: Seventy patients were included. Mean age was 85.30 (± 3.82) years, 57 % (n = 40) were female and about 32,90 % (n = 23) were DM. In the NDM patients SHR was positively correlated with CRP (r = 0.31, p = 0.03). In the APN group, SHR was positively correlated with CRP (r = 0.79, p < 0,01) in the NDM patients This is the first study of SHR impact in older patients.
Conclusions: SHR can have prognostic implications in hospitalized patients, mainly in those with PNA. Basing glycemic therapy on SHR should be considered in future studies, especially in geriatrics, as we stand before an ageing population in hospital wards.

Keywords: diabetes; stress hyperglycemia ratio; hyperglycemia; acute pyelonephritis; acquired community pneumonia; geriatric patients

Resumo

Introdução: A hiperglicémia está associada a maior morbilidade e mortalidade em doentes hospitalizados. O rácio de hiperglicemia de stresse (RHS) pode ser um marcador determinante do dano induzido pela hiperglicemia. O objectivo do estudo é clarificar a relação entre o RHS e os parâmetros clínicos e analíticos em doentes com pielonefrite aguda (PNA) ou pneumonia adquirida na comunidade (PAC).
Métodos: Estudo retrospectivo em doentes com idade superior ou igual a 80 anos. Dados clínicos e analíticos – critérios de síndrome de resposta inflamatória sistémica (SRIS); proteína C reactiva (PCR) (mg/L); taxa de filtração glomerular (TFG) (mg/dL/1,73m^2); tempo de internamento (dias). O RHS foi calculado através do quociente entre a glicémia em jejum do primeiro dia de internamento e a glicémia média estimada derivada da HbA1c. Os doentes foram divididos em dois grupos – diabéticos (DM) *versus* não diabéticos (NDM). Análises estatística foi feita usando o *software* SPSS versão 22.0.

> INTRODUCTION

Diabetes is considered a complex disease not only for its long duration, but also for the heterogeneity of its pathophysiology and the increased risk of complications, which requires effective management that can be difficult in older patients. In Europe, nearly a quarter of people with diabetes are older than 75 years old and available data is still unclear about specific complications of older patients. [1,2]

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Recebido/Received: 11/02/2021; Aceite/Accepted: 29/11/2021.

Resultados: Setenta doentes foram seleccionados através dos critérios de inclusão. A média de idades era de 85,30 (± 3,82) anos, 57 % (n = 40) eram mulheres e 32,90 % (n = 23) eram DM. Não foram encontradas correlações na amostra total, ou particularmente no grupo DM, enquanto que no grupo NDM o RHS correlacionava-se positivamente com a PCR (r = 0,31, p = 0,03). Nos doentes com PAC, quer o grupo DM quer o grupo NDM não mostraram achados relevantes. Considerando o grupo PNA, o RHS correlacionava-se positivamente com a PCR (r = 0,79, p < 0,01) nos doentes NDM, enquanto que nos doentes DM não foram encontrados resultados com significância estatística.
Conclusões: O RHS pode ter implicações prognósticas nos doentes hospitalizados, especialmente no contexto de PNA. A terapêutica glicémica baseada no RHS deve ser considerada em estudos futuros, especialmente em geriatria, uma vez que representa uma grande parte dos doentes em enfermaria.

Palavras-chave: diabetes; rácio de hiperglicémia de stresse; hiperglicémia; pielonefrite aguda; pneumonia adquirida na comunidade; geriatria

Hyperglycemia is associated with higher morbidity and mortality rates in hospitalized patients with critical illness, as chronic obstructive airway disease, myocardial infarction and other acute conditions. Historically, it has been linked only to diabetic patients, but recent studies revealed that the risk of de novo hyperglycemia is far more important. Besides, older people have higher prevalence of comorbidities that affect their homeostasis, such as glycemic control, and may be in greater risk for developing diabetes *mellitus* type 2. [3-10]

In critically ill patients, stress-induced hyperglycemia (SIH) is related to excessive levels of anti-inflammatory cytokines, which contribute to adverse outcomes, through induction of endothelial dysfunction or oxidative stress. Stress hormones, as glucagon, cortisol, catecholamines, and growth hormone, are also augmented. This results in increased insulin resistance and gluconeogenesis. (11) So, it was hypothesized SIH could also become a prognostic marker for general acute illness and its determination would influence further reduction in morbidity and mortality. However, limitations in SIH have been identified. Research data on SIH usually determines absolute glucose concentration only at admission, which, itself, could be due to a chronic high baseline serum glucose level. Else ways, variations of baseline glycemia may become more accurate when establishing the relation between serum glucose and prognosis. [12]

A new index of relative hyperglycemia, firstly proposed by Roberts et al., stress hyperglycemia ratio (SHR), can be a more valuable marker of SIH and acute distress, as it considers background glycemia. [3] Despite being suggested as a better predictive marker for critical illness, we question if SHR results from a combined effect of sample heterogeneity or if it acts as a surrogate for other confounding variables. Then, SHR should be tested for specific acute conditions, as infections, in order to assess its validity. As older patients are frequently excluded from acute severity illness studies and our population is ageing, special focus should be applied on this particular group.

The main objective of this study is to clarify the relationship between SHR and clinical/analytical markers of severity disease in patients with acute pyelonephritis (ANP) or community acquired pneumonia (CAP), 80 years or older, either diabetic or non-diabetic.

> METHODS

This is a retrospective study held in an internal medicine ward. We analyzed clinical data from patients admitted due to APN or CAP. APN was defined as an infection of the renal pelvis and kidney resulting from ascent of a bacterial pathogen up the ureters from the bladder to the kidneys, with isolation in uroculture. For CAP we used 2007 Infectious Diseases Society of America/American Thoracic Society Criteria for Defining Community--acquired Pneumonia.

This selection was based on its usual frequency in hospital geriatric admissions and particular prevalence on our sample. The hallmark for our sample was determined after determination of mean age of all patients admitted on our internal medicine ward: 79,8 years.

Inclusion criteria included patients 80 years or older admitted in internal medicine ward for APN or CAP (according to the International Classification of Diseases 10th edition) from January 2015 to December 2017. Exclusion criteria included missing data for HbA1c, fasting serum glucose (FSG) at first day of admission, CRP or GFR. Patients with conditions affecting HbA1c levels were also excluded (overt renal failure, hemodialysis or peritoneal dialysis, kidney transplantations recipients or anemia – defined as hemoglobin < 10g/dL). Finally, all patients younger than 80 years old or those who were institutionalized or bedridden were also excluded. Once personal data was involved, anonymization of the dataset was made as patients were being introduced in the study.

Demographic data included age and gender. Clinical and laboratory data comprised systemic inflammatory response syndrome (SIRS) criteria – tympanic temperature < 36ºC or > 38ºC, heart rate > 90 beats per minute;

leukocytes count < 4x109/L or > 12x109/L; respiratory rate > 20 cycles per minute or pCO2 in arterial blood > 32mmHg; C-reactive protein (PCR) (mg/L); glomerular filtration rate (GFR) (mg/dL/1.73m^2); length of stay, in days. In-hospital mortality rate was also determined.

Patients were divided in two major groups: non-diabetic (NDM) – if HbA1c lower than 6,5% and no diagnosis of diabetes *mellitus* – and diabetic (DM) – if HbA1c was equal or higher than 6,5% or previous diagnosis of diabetes *mellitus*. Then, another distinction was made between CAP and APN patients. SHR was defined according to Roberts *et al.* as the quotient between FSG obtained and the average serum glucose calculated from HbA1c value: [glucose (mg/dL /18]/ [(1.59 x HbA1c) – 2.59].

Descriptive statistics were determined and analysis of variance was made with one-way ANOVA. To assess the strength and direction of the obtained associations, Pearson correlation coefficients were later calculated and a corresponding dispersion matrix was made. Wilcoxon tests and logistic regression were also employed. All statistical analyses were performed with statistical package SPSS V.22.0 with a two-tailed P value of 0.05 considered statistically significant.

> RESULTS

DM and NDM Population

During the 2 years period of analysis, 844 patients were admitted, but only 70 met the inclusion criteria - 774 were excluded due to missing or conflicting data. Patients' characteristics are revealed in Table I. Mean age was 85.3 (± 3.8) years, 57 % (n=40) were female and about 32.9 % (n = 23) were DM. Patients in DM group had a FSG level higher than the patients in NDM group (228.8 *vs.* 162.6 mg/dL, p < 0.01). No reported deaths among included patients, resulted in a mortality rate equal to zero. Between these two major groups, there were no statistically significant differences in age (85.4 *vs.* 85.3 years, p=0.96), GFR (72 *vs.* 87.6 mg/dL/1.73m^2, p = 0.67), CRP (91.9 *vs.* 108.8 mg/L, p = 0.77), mean value of SIRS criteria (1.7 *vs.* 1.7, p = 0.98) or length of stay (9.4 *vs.* 12.9 days, p = 0.50) SHR was positively associated with GFR (r = 0.06, p = 0.60), CRP (r = 0.14, p = 0.26), mean value of SIRS criteria (r = 0.12, p = 0.32) and length of stay (r = 0.17, p = 0.16), but none of these correlations were considered as statistically significant.

Regarding the DM group, SHR was positively correlated with GFR (r = 0.23, p = 0.28), CRP (r = 0.23, p = 0.29), average value of SIRS criteria (r = 0.24, p = 0.28) and length of stay (r = 0.07, p = 0.77), but not statistically significant. In the NDM group, SHR was positively correlated with CRP (r = 0.31, p = 0.03) with statistical significance. There were also positive correlations between SHR and GFR (r = 0.08, p = 0.60), mean value of SIRS criteria (r = 0.29, p = 0.051) and length of stay (r = 0.18, p = 0.23), but without statistical significance.

APN

In the APN population (n = 22), 81.8 % (n = 18) patients were female, with a mean age of 85 (± 3.9) years old, and 40.9 % (n = 9) were DM. Comparing DM and NDM groups, there were no statistically significant differences in age (84.9 *vs.* 85 years, p=0.99), FSG (256.7 *vs.* 164.6 mg/dL, p = 0.10), GFR (65.8 *vs.* 73 mg/dL/1.73m^2, p = 0.70), CRP (27 *vs.* 69.9 mg/L, p = 0.25), average value of SIRS criteria (1.2 *vs.* 1.3, p = 0.98) or length of stay (10.1 *vs.* 14.3 days, p = 0.83). Analyzing correlations between variables, SHR was positively associated with CRP (r = 0.60, p < 0.01) with statistical significance (Figure 1). There was also a positive correlation between SHR and GFR (r = 0.12, p = 0.60), mean value of SIRS criteria (r = 0.14, p = 0.53) and length of stay (r = 0.12, p = 0.59), but those were not considered statistically significant.

In the DM group, although there were positive correlations between SHR and CRP (r = 0.45, p = 0.22), GFR (r = 0.01, p = 0.97), mean value of SIRS criteria (r=0.14, p=0.72) and length of stay (r = 0.23, p = 0.56), none of them had statistical significance. In the NDM group, SHR was positively correlated with CRP (r = 0.79, p < 0.01) within the confidence interval (Figure 2). Albeit statistically insignificant, there was also positive correlation between SHR and GFR (r = 0.17, p = 0.58), mean value of SIRS criteria (r = 0.14, p = 0.64) and length of stay (r = 0.10, p = 0.74).

CAP

In the CAP population (n = 48), 45.8 % (n = 22) patients were female, with a mean age of 85.5 years (± 3.8), and 29.2 % (n =14) were DM. Comparing DM and NDM group, there was no significant difference in age (85.6 *vs.* 85.4 years, p = 0.98), FSG (210.9 *vs.* 161.9 mg/dL, p = 0.05), GFR (59.5 *vs.* 83.2 mg/dL/1.73m^2, p = 0.73), CRP (133.6 *vs.* 123.7 mg/L, p = 0.95), mean value of SIRS criteria (2.1 *vs.* 1.9, p = 0.90) or length of stay (8.9 *vs.* 12.4 days, p = 0.54).

As for correlation between variables, SHR positively correlated with GFR (r = 0.09, p = 0.55), mean value of SIRS criteria (r = 0.15, p = 0.31) and length of stay (r = 0.22, p

Table I - Baseline characteristics of subjects according to each group.

	DM and NDM population (n=70)				*APN (n=22)*				*CAP (n=48)*			
	Total	**DM**	**NDM**	***p***	**Total**	**DM**	**NDM**	***p***	**Total**	**DM**	**NDM**	***p***
Age (years)	85.3±0.46	85.4±0.8	85.3±0.6	N.S.	85.0±0.9	84.9±1.5	85±1.1	N.S.	85.5±0.6	85.7±0.9	85.4±0.7	N.S.
Male (%)	42.9	34.8	46.8	N.S.	18.2	11.1	23.1	N.S.	54.2	50	55.9	N.S.
Glucose (mg/dL)	184.4±9.3	228.8±19.9	162.6±8.5	**0.003**	202.3±21.5	256.7±31.8	164.6±24.9	N.S.	176.2±9.4	210.9±25.2	161.9±7.2	N.S.
HbA1c (%)	6.2±0.1	7.5±0.3	5.6±0.1	**<0.001**	6.5±0.3	7.9±0.5	5.6±0.1	**<0.001**	6.1±0.2	7.3±0.3	5.6±0.1	**0.05**
SHR	1.4±0.1	1.3±0.1	155±0.1	N.S.	1.5±0.1	1.4±0.2	1.5±0.2	N.S.	1.4±0.1	1.3±0.1	1.4±0.1	N.S.
CRP (mg/L)	103.3±10.8	91.9±21.9	108.8±12.2	N.S.	52.4±12.8	27.0±9.6	69.9±19.5	N.S.	126.6±13.5	133.6±30.9	123.7±14.4	N.S.
GFR CKD-EPI (mL/min/1.73m^2)	86.3±2.7	82±4.8	88.5±3.2	N.S.	84.0±4.0	75.8±7.1	87.0±4.7	N.S.	83.4±10.4	79.5±6.6	86.7±4.0	N.S.
Hypertension (%)	84.3	91.3	80.9	N.S.	81.8	88.9	76.9	N.S.	85.4	92.9	82.4	N.S.
Hypercholesterolemia (%)	42.9	43.5	42.6	N.S.	40.9	33.3	46.2	N.S.	43.8	50	41.2	N.S.
Current smoking (%)	12.9	13.0	12.8	N.S.	9.1	22.2	0	**<0.001**	14.6	7.1	17.6	N.S.

Data are expressed as the means ± standart deviation. Bold data indicate significance at p <0.05.
DM, diabetic patients; NDM, non-diabetic patients; APN, acute pyelonephritis; CAP, community acquired pneumonia; SHR, stress hyperglicemia ratio; CRP, c reactive protein; GFR CKD-EPI, glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration

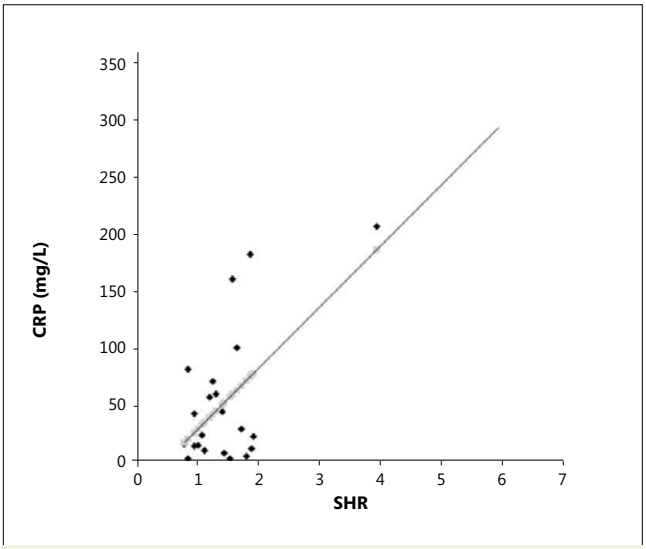

Figure 1 - Correlation between SHR and CRP in patients with APN.

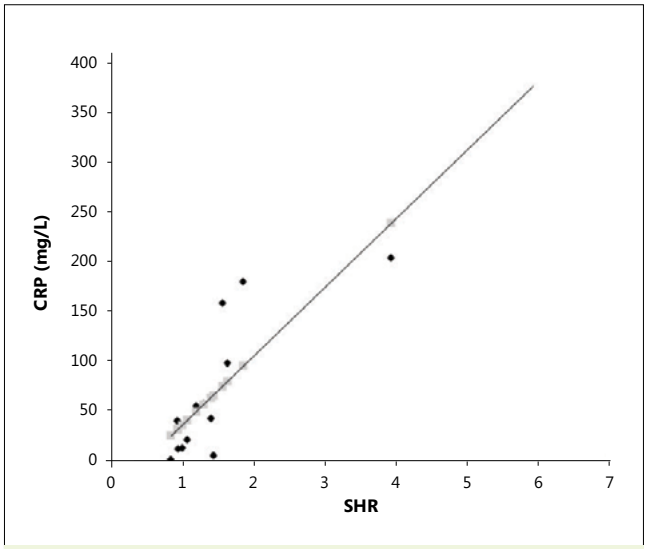

Figure 2 - Correlation between SHR and CRP in NDM patients with APN.

= 0.13); there was no correlation between SHR and CRP. None of the above findings revealed statistical significance.

Considering the DM group, SHR was positively correlated with CRP (r = 0.15, p = 0.60), GFR (r = 0.41, p = 0.15), mean value of SIRS criteria (r = 0.34, p = 0.24) and length of stay (r = 0.17, p = 0.57), but those associations were not statistically significant. As for the NDM group, SHR was found to be positively correlated with CRP (r = 0.11, p = 0.54), GFR (r = 0.12, p = 0.50), length of stay (r = 0.28, p = 0.11) and mean value of SIRS criteria (r = 0.46, p <0.01), the latter being statistically significant.

> DISCUSSION

The relationship between hyperglycemia on admission and disease outcomes has been established on previous studies, as mentioned above. However, the link between SIH – when considered as absolute FPG - and acute disease outcome is complex, and some studies argue that underlying disorders as diabetes or glucose intolerance may account for those positive findings. SHR relates to background glycemia and so it is suggested as a better biomarker for critical illness than absolute glycemia. As glucose and HbA1c tests are widely available, SHR is easily determined, which could turn this ratio on useful and simple prognostic marker. [3-15]

Since Robert *et al*. study, further evidence has been published testing SHR as a marker of SIH in specific conditions, such as myocardial infarction and chronic obstructive pulmonary disease. Although these reports included large sample populations, none has considered the elderly alone or studied PNA or CAP, which are prevalent acute disorders, especially in older patients. Regarding the results of DM and NDM populations, differences between FSG levels turned as expected, being higher in diabetic patients. In the whole sample, there were no significant differences in the analyzed variables or in its correlations.

SIRS was introduced by Bone and colleagues with the goals of improving the early detection of patients with sepsis, facilitating standardization of research protocols, and providing useful prognostic information. Since that time, the SIRS criteria have been widely adopted in both research and clinical practice as a prognostic tool.

Focusing each major group separately, DM patients had no statistically significant correlations between SHR and GFR, CRP, SIRS criteria or length of stay, although the positive results could suggest a possible tendency. Contrarily, NDM patients revealed a positive and statistically significant correlation between SHR and CRP, which further corroborates the assumption that patients without previous diabetes diagnosis may be more predisposed to SIH and its deleterious effects. [3,16]

Looking at PNA group results, one can further ascertain the later statement. Considering DM and NDM patients, SHR was positively correlated with CRP and also presented this association with the other variables, showing once more a possible tendency. Considering only PNA NDM patients, the correlation between SHR and CRP becomes stronger, opposed to DM group. In both groups, there is a positive tendency between SHR and

the other variables. In the CAP group, neither the total nor DM or NDM showed any statistically significant results, although there was a positive association tendency between SHR and CRP, SIRS criteria, GFR and length of stay.

This opposite findings in PNA *versus* CAP may be explained by the role of kidneys in the physiology of glucose metabolism. Renal glucose production contributes approximately to 25% of systemic glucose production, while renal glucose uptake accounts for 20% of systemic glucose removal. An important consequence of hyperglycemia in critical illness is insulin resistance and glucose production and transport alterations. Glucose metabolism in kidneys is regulated by insulin, and loss of metabolic function could account for insulin resistance as a result of organ failure. Moreover, uremia is also associated with decreased kidney uptake of glucose and reduction in peripheral glucose transporters. [17]

GLUT1 is responsible for the facilitated uptake of glucose in many tissues, as the kidneys, and cells internalize these proteins when exposed to hyperglycemia. However, in SIH, not only GLUT1 is not internalized but it is also overexpressed, leading to glucose overload. Many pathways are proposed to explain these events, like the action of various cytokines (IL-6 and TNF-alpha) and nitric oxide production, oxidative stress and hyperlipidemia. A large multicenter study analyzed patients with acute kidney injury (AKI) and found that insulin resistance is common, and the degree of hyperglycemia correlated with mortality. Additional observational studies from different populations suggest a link between hyperglycemia and metabolic syndrome on AKI development. However, further research is needed to explain whether these associations are a consequence of deranged metabolic responses inherent to critical illnesses or if there is a direct effect of hyperglycemia and insulin resistance on the kidney. [18-20]

Our study has some limitations. First, it was a retrospective study, with a small sample, which may be subjected to selection bias and particular population epidemiologic characteristics. We're aware that groups stratification in DM/NDM or PNA/CAP further reduced the statistic relevance of our findings, but clinical correlations seemed priority. Second, we didn't take into account ongoing medication, which can be particularly relevant as some patients in CAP group had COPD on glucocorticoids, which would falsely increase glycemia. Third, hyperglycemia control may have influenced the outcomes, as the established treatment protocol wasn't always accomplished.

The great achievement of our study relies on focusing about SHR not only in a geriatric population, but specifically in PNA and CAP, which are such prevalent infections leading to elderly admission. Besides, we strongly insisted on a careful selection of patients and strictly application of inclusion and exclusion criteria. It's our belief that a prospective study that takes into account other variables such as glycemic management, glucocorticoids dosage, serum insulin levels and insulin resistance ratios should be performed. This could help to clarify the pathophysiology of SIH and its implications, as SHR could be a surrogate from other unincluded variables. Moreover, other studies are needed to assess whether SHR has a treatment monitoring role and how it acts in homeostatic metabolism of insulin, particularly in diabetic patients. We believe that SHR can actually change the paradigm of diabetes management in hospitalized patients.

In conclusion, SHR is a useful and easily applicable biomarker, with prognostic implications in the elderly. In this study, we identified a strong relationship between SHR and inflammatory markers in PNA. Future research should focus on whether basing glycemic therapy on SHR, rather than FPG, could improve elderly patients outcomes and its relevance in the post hospital discharge influence on diabetes development. <

Conflicts of interest/*Conflitos de interesse:*

The authors declare that they have no conflicts of interest/*Os autores declaram não haver conflitos de interesse.*

Confidentiality of data/*Confidencialidade de dados:*

The authors declare that no patient data appears in this article/*Os autores declaram que nenhum dado relativo aos doentes aparece neste artigo.*

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