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HYPERGLYCAEMIA IN CRITICAL ILLNESS IN NON-DIABETICS IS ASSOCIATED WITH INCREASED INTRINSIC INSULIN RESISTANCE

HIPERGLIKEMIJA U KRITIČNO OBOLJELIH BOLESNIKA BEZ DIJAGNOZE ŠEĆERNE BOLESTI POVEZANA JE S POVEĆANOM INZULINSKOM REZISTENCIJOM

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Abstract

Introduction: Hyperglycemia commonly occurs in the course of critical illness, both in patients with and without apparent glucose metabolism disorder. Insulin resistance is characterized by the reduced response of tissues to insulin. We hypothesized that one of the causes of hyperglycemia in critical illness among patients without apparent glucose metabolism disorder is intrinsically increased insulin resistance.

Patients and methods: Patients with no history of impaired glucose metabolism admitted to a medical intensive care unit due to critical illness were included. They were divided into hyperglycaemia group (glucose >7.7 mmol/l, on at least two occasions) and normoglycaemia group. Glycated hemoglobin during hospital stay and oral glucose tolerance test within 6-8 weeks after discharge were performed, patients with unknown diabetes or pre-diabetes were excluded. On the follow up visit 6-8 weeks after discharge insulin resistance was assessed by indirect methods using simple indices: QUICKI, HOMA-IR, log HOMA-IR and HOMA2-IR.

Results: Research was concluded on 221 patients: 114 in hyperglycaemia group and 107 in normoglycaemia group. There were no significant differences in age nor sex among groups. BMI, WHR and positive family history of type 2 diabetes had higher values in hyperglycaemia group. Patients in hyperglycaemia group had higher insulin levels (75.5 pmol/l vs 62.8 pmol/l, p<0.001) and higher insulin resistance assessed by simple insulin resistance indices compared with patients in normoglycaemia group. Multivariate logistic regression analysis showed independent association of BMI, WHR, HOMA-IR and QUICKI with occurrence of hyperglycemia in acute illness.

Conclusion: Occurrence of hyperglycemia in critical illness among patients without apparent glucose metabolism disorder is associated with intrinsically increased insulin resistance.

Key words: hyperglycaemia in critical illness; insulin resistance; prediabetes

Sažetak

Uvod: Hiperglikemija je česta pojava tijekom teške akutne bolesti i u bolesnika sa šećernom bolesti, ali i u bolesnika bez očitog poremećaja metabolizma glukoze. Inzulinska rezistencija karakterizirana je smanjenim odgovorom tkiva na inzulin. Naša hipoteza bila je da je intrinzička inzulinska rezistencija jedan od čimbenika koji dovodi to evidentnog poremećaja glikemije u teškoj akutnoj bolesti.

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Bolesnici uključeni u studiju nisu imali anamnezu poremećaja metabolizma glukoze i primljeni su u internističku jedinicu intenzivne medicine zbog teške akutne bolesti. Podijeljeni su u dvije skupine: hiperglikemijsku skupinu (glukoza >7,7 mmol/l u najmanje dva navrata) i normoglikemijsku skupinu. Glikirani hemoglobin (A1c) tijekom hospitalizacije, te oralni test tolerancije glukoze provedeni 6-8 tjedana nakon otpusta korišteni su za isključivanje bolesnika sa šećernom bolešću koja nije bila prepoznata prije hospitalizacije. Na kontrolnom pregledu 6-8 tjedana po otpustu određena je inzulinska rezistencija pomoću indirektnih metoda: QUICKI, HOMA-IR, log HOMA-IR i HOMA2-IR.

Rezultati: Istraživanje je uključilo 221 bolesnika: 114 u skupini hiperglikemije, 107 normoglikemičnih. Nije bilo statistički značajne razlike u spolnoj raspodjeli i dobi između skupina; hiperglikemijska skupina imala je viši indeks tjelesne mase, viši omjer struka i bokova te češće pozitivnu obiteljsku anamnezu za tip 2 šećerne bolesti. Bolesnici u hiperglikemijskoj skupini imali su više razine inzulina (75.5 pmol/l) u usporedbi s normoglikemijskom skupinom (62.8 pmol/l; p<0.001) te više razine inzulinske rezistencije mjerene bilo kojom metodom. Multivarijatna analiza logističkom regresijom pokazala je neovisnu povezanost indeksa tjelesne mase, omjera struka i bokova, HOMA-IR i QUICKI s pojavom hiperklikemije akutne bolesti.

Zaključak: Pojava hiperglikemije akutne bolesti u bolesnika bez evidentnog poremećaja metabolizma glukoze povezana je s povišenom intrinzičkom inzulinskom rezistencijom.

Ključne riječi: hiperglikemija u akutnoj bolesti; predijabetes; inzulinska rezistencija

Introduction

Hyperglycaemia commonly occurs during the course of any critical illness: regularly among patients with diabetes or pre-diabetes, but also in patients without apparent glucose metabolism disorder. It is associated with worse clinical outcomes including morbidity, mortality and length of hospital stay, infection and overall complication rates (1-7). Also, non-diabetics who developed hyperglycaemia in critical illness should be considered as a population at increased risk for developing diabetes (8-14).

Insulin resistance is characterized by reduced response of tissues to insulin. It is a crucial part of metabolic syndrome, a key factor in development of type 2 diabetes, closely linked to obesity and is an underlying cause of cardiovascular and neurodegenerative diseases (15-17). Its inheritance is somewhat elucidated by genome wide association studies (GWAS) (18).

Despite the fact that stress and inflammatory response occur among all critically ill patients, evident hyperglycaemia is not encountered in all of them. We hypothesized that the predisposition for hyperglycaemia in critical illness among patients without apparent glucose metabolism disorder lies in previously developed insulin resistance of those patients.

Patients and methods

This was a prospective observational study performed in the medical intensive care unit (ICU) of the University Hospital Centre Zagreb.

Adult patients with negative history of diabetes mellitus (DM), impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) admitted to the ICU due to critical illness were included. The term critical illness in this study covered a spectrum of diseases, the most common being acute coronary syndrome, sepsis and septic shock, pneumonia and lung oedema, which represent most common admission diagnosis in our ICU. Negative history of existing glucose metabolism disorders was confirmed with HbA1c measurement and oral glucose tolerance test (OGTT) performed 6-8 weeks after hospitalization.

Patients who were diagnosed with glucose metabolism disorder (DM, IFG, IGT) during hospitalization or at the follow-up visit were excluded from the study. Patients with glucocorticoid treatment during or 8 weeks before admission, those with known endocrine disorder that might alter glucose metabolism, and those with end-stage disease were also excluded from the study. We did not include patients who were unwilling to participate and those with acute or chronic condition that might cause early fatality or hinder follow up.

The following data were collected for all patients: age, sex, body mass index (BMI), family history of diabetes, history of smoking, serum cholesterol and triglycerides concentrations. Admission Acute Physiology and Chronic Health Evaluation (APACHE II) and waist to hip ratio (WHR) were calculated for all patients (19,20), Sequential Organ Assessment Score (SOFA) was scored daily and the

highest score was used as a measure of disease severity (21,22). Plasma glucose (venous) was measured at least twice daily (6 A.M. and 6 P.M.). Additional measurements were performed in patients whose blood glucose was variable or in cases where insulin was administrated to treat hyperglycaemia. Plasma glucose concentration was analyzed with enzymatic method-photometry UV with hexokinase on Cobas c501/c311, Roche device or using point-of-care analyzer (IL GEM Premier 3000 Electrolyte Analyzer, Instrumentation Laboratories, Lexington, MA, USA).

Patients were fed according to the Department policy with target caloric intake set on 15 kCal/kg/day. Enteral nutrition was started not later than 24 hours after admission, in cases where enteral nutrition was not tolerated or contraindicated, parenteral nutrition was performed.

According to the measured glucose levels patients were divided in two groups: hyperglycaemia group and normoglycaemia group. The hyperglycaemia group was comprised of patients whose glucose level was at least in two occasions higher than 7.7 mmol/l (140 mg/dL). All other patients formed the normoglycaemia group.

Patients included in the study had a follow-up visit performed 6-8 weeks after hospital discharge, during which fasting blood samples were collected and OGTT was performed according to WHO recommendation (23). Fasting blood samples of patients with normal OGTT values were centrifuged and the serum was stored in refrigerator settings of -20 °C. Serum insulin concentration was gained through electrochemiluminescence method on Cobas E 601, Roche device, with Roche Elecsys/E170 test (Roche Diagnostics, Indianapolis, Indiana). Insulin resistance was expressed with simple insulin resistance indices: QUICKI (24), HOMA-IR (25,26), log HOMA-IR, HOMA 2-IR, HOMA 2-%S. HOMA 2-IR, HOMA 2-%S and beta cell function (HOMA 2%-B) were derived through the same HOMA2 computer model (27).

Definitions

Impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus (DM) were defined according to the ADA criteria (28). Sepsis, severe sepsis and septic shock were defined according to the usual criteria (29,30). Acute coronary syndromes were defined according to the ACC/AHA criteria (31-33).

Statistical analyses

MedCalc 22.017 and SPSS 17.0 were used for all statistical analyses. Categorical data are presented as absolute and relative frequencies, continuous variables as median with standard deviation. Chi square test was used for categorical variable while Student's t-test was used for continuous variables. Multivariate logistic regression analysis was performed using logistic regression. Statistical significance was set at $\alpha = 0.05$.

The study was approved by the Ethics Committee of the University Hospital Centre Zagreb. All patients included in the study signed an informed consent form. The study was not funded or supported by any organization, group or individual.

Table 1. Characteristics of patients included in the study

	All patients (N=221)	Patients with hyperglycaemia (N=114)	Patients without hyperglycaemia (N=107)	P
Age (years)	51±14	51±15	50±13	0.605
Female sex (N, %)	87 (39%)	41 (36%)	46 (43%)	0.784
Body mass index (kg/m2)	27±4	28.4±4.6	26.4±3.4	0.002
Waist to hip ratio	1.05±0.13	1.07±0.11	0.99±0.11	<0.001
Total cholesterol (mmol/L)	4.6±0.97	4.7±1.0	4.5±0.9	0.300
Triglycerides (µmol/L)	3.2±1.1	3.1±1.1	3.2±1.0	0.165
Highest glucose level in acute illness (mmol/L)	8.1±3.7	9.3±4.1	6.9±3.2	0.005
APACHE II score	18.4±3.9	19.5±4.9	17.3±3.7	0.001
SOFA score	3.1±0.6	3.2±0.6	2.8±0.5	0.003
Family history of DM (%)	54 (24.4%)	34 (32.7%)	20 (18.7%)	0.029
Smoking	50 (22.6%)	28 (26.9%)	32 (27.3%)	0.936

APACHE: Admission Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Assessment; DM: diabetes mellitus

Hyperglycemia is prevalent in critical illness, particularly among patients with diabetes or pre-diabetes, but it can also occur in those without any obvious glucose metabolism disorders.

Results

The study included a total of 221 patients: 114 in hyperglycaemia group and 107 in normoglycaemia group. There were no statistically significant differences in age or sex between the two groups. Body mass index, waist-to-hip ratio and positive family history of DM were significantly higher among patients in hyperglycaemia group (Table 1).

APACHE II and SOFA scores were higher in the hyperglycemia group, but multivariate logistic regression analysis did not point those scores as independent predictors of hyperglycaemia occurrence. Patients who developed hyperglycaemia during critical illness had higher insulin resistance according to all simple indices of insulin resistance: QUICKI, HOMA-IR, log HOMA-IR, HOMA 2-IR, as shown in Table 2.

On the follow-up visit patients from hyperglycaemia group had higher fasting glucose level (4.7 mmol/l vs. 4.6 mmol/l), but that difference did not show as statistically significant (p=0.414). Fasting insulin level was higher in the hyperglycaemia group (75.5 pmol/l vs 62.8 pmol/l), p<0.001. Function of beta cell did differ among the groups with higher values in hyperglycaemia group (141.9 vs 130.7), but the difference was not statistically significant (p<0.07).

Multivariate analysis with logistic regression (Table 3) pointed out independent correlation between body mass index and waist-to-hip ratio with occurrence of hyperglycaemia in critical illness. It also showed independent correlation of both HOMA-IR and QUICKI with hyperglyceamia in critical illness.

Table 2. Insulin resistance of patients included in the study

	Patients with hyperglycaemia (N=114)	Patients without hyperglycaemia (N=107)	P
Glucose level (mmol/L)	4.7 ± 0.5	4.6 ± 0.56	0.414
Insulin (pmol/L)	75.5 ± 16.1	62.8 ± 11.0	<0.001
QUICKI	0.339 ± 0.009	0.349 ± 0.006	<0.001
HOMA-IR	2.245 ± 0.417	1.839 ± 0.224	<0.001
Log HOMA-IR	-0.244 ± 0.079	-0.268 ± 0.053	<0.001
HOMA 2-IR	1.37 ± 0.27	1.14 ± 0.17	<0.001
HOMA 2-%B	141.9 ± 47.9	130.7 ± 43.5	0.070
HOMA 2-%S	75.7 ± 15.2	89.5 ± 13.4	<0.001

Disscusion

The group of patients who developed hyperglycaemia in critical illness has statistically higher level of insulin resistance after hospitalization according to all simple indices in comparison with the group of patients which remained normoglycaemic during critical illness.

Since the definition of hospital acquired hyperglycaemia was not universal at the moment we started the study threshold was set on 7.7 mmol/l (140 mg/dL). This cut-off value was taken from previous studies dealing with occurrence of hyperglycaemia in critical illness among non-diabetics (10).

Study design with strict inclusion/exclusion criteria and 6-8 weeks delay until insulin resistance measurements aimed to assure insulin resistance was not elevated due to acute illness or pre-existing diabetes

Feeding regimen and caloric intake could have played a role in development of hyperglycaemia, but it did not differ between the groups in caloric intake nor in feeding strategy.

Patients who developed hyperglycaemia during critical illness showed higher insulin resistance after hospitalization, suggesting that intrinsic insulin resistance is a key contributor to hyperglycaemia. This highlights the role of metabolic factors in the development of hyperglycaemia in critically ill patient

Positive family history of diabetes was more often in hyperglycaemia group. Due the importance of family history in diabetes (34) and insulin resistance being known part of the disease progression (15), it was not surprising to find patients genetically predisposed to diabetes in the group with intrinsically increased insulin resistance which developed hyperglycaemia during the critical illness.

Higher BMI and waist-to-hip ratio were seen among the hyperglycaemia group patients. These results were expected due to diabetes- obesity relationship (35,36).

Hyperinsulinemic euglycemic clamp (HEC) is the gold standard for the measurement of insulin sensitivity, but surrogate indices used in this study (QUICKI, HOMA-IR) seem to be appropriate to assess insulin resistance (37-39).

Relatively small number of medical ICU patients involved in the study represents its strongest limitation. Even though we expect same results among patients without glucose metabolism disorder hospitalized in surgical ICU who developed hyperglycaemia in critical illness, in the future research should be broaden to those patients as well.

We suggest that increased levels of the intrinsic insulin resistance are a major contributor of hyperglycaemia in

Table 3. Independent predictors of hyperglycaemia occcurrence in multivariate logistic regression analysis

Variable	OR (95% CI)	P
BMI, for each increase of 1.0 kg/m2	1.23 (1.11 – 1.36)	0.001
WHR, for each increase of 0.1	2.56 (1.79 – 3.64)	<0.001
HOMA-IR, for each increase of 0.1	6.58 (1.59 – 27.34)	0.036
QUICKI, for each change of 0.01	25.1 (1.25 – 49.8)	0.041

BMI: body mass indeks; WHR: waist to hip ratio

critical illness. Like survivors from ICU who had transitory hyperglycaemia, women with a history of gestational diabetes (GDM) are in risk for future type 2 diabetes (40). These women are shown to be more insulin resistant (41,42).

Higher body mass indeks, waist-to-hip ratio, and a family history of diabetes were more common in the hyperglycaemia group, indicating a predisposition to insulin resistance and diabetes.

We hypothesize that metabolic disorder which makes some individuals prone to hyperglycaemia in critical illness (10) involves increases already relatively high insulin resistance what makes compensation by enhanced beta cell function more difficult, especially if beta cells have some degree of disfunction (15). We may conclude that hyperglycemia in critical illness reveals increased insulin resistance and predisposition for later development of diabetes.

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