Commentary

Hyperglycemia in septic patients: an essential stress survival response in all, a robust marker for risk stratification in some, to be messed with in none

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Submitted Apr 20, 2016. Accepted for publication Apr 27, 2016.
doi: 10.21037/jtd.2016.05.24
View this article at: http://dx.doi.org/10.21037/jtd.2016.05.24

Since the very beginning of medicine the relation between glucose and illness has been of interest to physicians, as already Hippocrates stated: "*Si quis febricitanti cibum det, convalescent quidem, robur: aegrotanti vero, morbus fit.*" (That nutrition, which is beneficial in the stage of convalescence from fever, would be truly injurious during the prevalence of the disease).

More recent van Vught *et al.* have investigated the relation of admission hyperglycemia in patients suffering from sepsis (1). In a sub-study of a prospective observational study they found that severe hyperglycemia (>200 mg/dL) but not mild hyperglycemia (141–199 mg/dL) at admission was associated with increased 30-day mortality [HR 1.66; 95% confidence interval (CI): 1.24–2.23]. This was true for both patients with known diabetes and without diabetes, which is in contrast to previous findings by e.g., Stegenga *et al.* who reported an association of hyperglycemia with mortality only in patients without diabetes (2).

In a data set of medical critically ill patients of our own (retrospective, single-center data, 7,851 patients, 659 suffering from diabetes, 4,093 males, 522 admitted for sepsis, *Table 1*) severe hyperglycemia (>200 mg/dL) was associated with increased intra- intensive care unit (ICU) mortality (HR 1.94, 95% CI: 1.63–2.32; P<0.001; 10.4% *vs.* 18.4%) in the overall cohort and for patients without (10.1% *vs.* 20%; HR 2.22; 95% CI: 1.83–2.69) type 2 diabetes mellitus but not with known diabetes (12.8% *vs.* 13.0%; P=0.50). But interestingly, severe hyperglycemia (>200 mg/dL) was not associated with intra-ICU mortality in the sub-cohort of patients admitted to our ICU for sepsis (40% *vs.* 40%; P=0.926), regardless of the medical history of pre-existing diabetes (*Table 2*). Mortality in our sub-cohort of septic patients was with 40% intra-ICU mortality higher than in the patients suffering from sepsis investigated by van Vught *et al.*, as overall mortality was only 27.1% in that study. We speculate that our collective was clinically sicker and in patients with septic shock even a beneficial association between hyperglycemia and mortality is in accordance to literature (3).

Of note, van Vught *et al.* further propose that the association of hyperglycemia and mortality is unrelated to exaggerated inflammation, endothelial cell activation and coagulation as severe hyperglycemia was associated with a decreased acute phase protein and cytokine response as well as an attenuated reduction in anticoagulant proteins such as protein C and antithrombin. This finding is surprising and new as it was thought and shown e.g., by Leonidou *et al.* that hyperglycemia is associated with increased pro-inflammatory cytokine production in septic patients (4).

In stress situations the body is thought to activate the central nervous system and neuroendocrine axes which release hormones such as catecholamines, glucagon and cortisol which are known to stimulate hepatic glucose production and lead to hyperglycemia (5). Stress hyperglycemia is primarily caused by hepatic gluconeogenesis and glycogenolysis rather than by peripheral insulin resistance (6). Further, hyperglycemia is thought to be at least partially physiologic and reasonable for the organism

Table 1 Baseline characteristics of 7,851 critically ill patients (4,093 males, 522 admitted for sepsis) admitted to a ICU of a tertiary care hospital: depending on blood glucose at admission (cut-off 200 mg/dL) we split our collective in two cohorts above and below the cut off

Baseline characteristics	Glucose >200 mg/dL	Glucose <200 mg/dL	P
Age (years)	68±12	64±15	<0.001
Duration of ICU stay (h)	110±154	81±123	<0.001
Lactate (mmol/L)	3.67±4.60	2.89±2.86	<0.001
Heart frequency (bpm)	106±24	100±23	0.4
White blood count (G/l)	13.96±12.23	11.60±10.25	<0.001
Known type 2 diabetes	24%	10%	<0.001

ICU, intensive care unit.

Table 2 Severe hyperglycemia (>200 mg/dL) was associated with increased mortality in the overall cohort (HR 1.94, 95% CI: 1.63–2.32; P<0.001) and in patients without pre-existing diabetes (HR 2.22, 95% CI: 1.83–2.69; P<0.001) but not in patients with known type 2 diabetes mellitus and in patients admitted for sepsis

Groups	HR	95% CI	P	Intra-ICU mortality, glucose <200 mg/dL (%)	Intra-ICU mortality, glucose >200 mg/dL (%)
Overall cohort	1.94	1.63–2.32	<0.001	10	18
Type 2 diabetes	1.03	0.65–1.62	0.5	12	13
Without type 2 diabetes	2.22	1.83–2.69	<0.001	10	20
Admitted for sepsis	1.29	0.79–2.09	0.32	40	40

HR, hazard ratio; CI, confidence interval; ICU, intensive care unit.

from a survival standpoint: Glucose is essential for all cells and glucose uptake is entirely dependent on a concentration gradient (though facilitated by transporters such as GLUT). In conditions like sepsis, shock or ischemia there is hypo-perfusion and reduced blood flow, therefore glucose must overcome interstitial space to reach its target, i.e., an under-perfused cell. In a situation like this a higher glucose concentration in the root, i.e., hyperglycemia, has to be considered adaptive to hypo-perfusion (7). Therefore, it is of particular interest that in the study of van Vught *et al.* hyperglycemia remained associated with mortality after correction for hyperlactatemia (HR 1.52; 95% CI: 1.1–2.1) in the overall cohort but not in patients without known diabetes. This could be interpreted within the meaning of a tight association of hypo-perfusion leading to hyperlactatemia and adaptive hyperglycemia in patients with a healthy glucose balance—with the relation of hypo-perfusion and hyperglycemia even excelling the association of hyperglycemia and immunological host response. Of note, the study was not optimal in regard to investigate the relation between hyperlactatemia and hyperglycemia as these values were not determined simultaneously. It certainly would be a worthy endeavor to investigate the particular relation between tissue hypo-perfusion, lactate and glucose at admission in critically ill patients.

In consistence with previous reports (8) Van Vught *et al.* report that preexisting diabetes did not influence 30-day mortality (30.3% *vs.* 26.2%; P=0.27), which we can further support by a similar finding regarding intra-ICU mortality in our own data set for both the overall cohort (11.9% *vs.* 12.0%, P=0.906) and septic patients (40.0% *vs.* 46.1%; P=0.32). This might be in contradiction to common perception as patients with diabetes mellitus are known to have an increased risk of sepsis (9), diabetes was observed to be associated with a common infectious disease (tuberculosis) as early as a thousand years ago by Avicenna (10) and diabetes is thought to be associated with an abnormal host response, impaired neutrophil chemotaxis and humoral defects (11-13). We speculate that this diminished unfavorable effect of diabetes at least in short

term is most probably due to better medical intensive care treatment and effective antibiotic treatment which outplays subtler immunologic defects by diabetes.

For the clinician glucose is more than a lab value for risk stratification but a parameter which easily can be influenced by application of insulin, glucose or glucagon. Therefore, it is a question of substance how we can optimize glucose management of our patients to accomplish optimal outcome for our patients.

In 2001, van den Berghe *et al.* published a startling study suggesting a favorable effect of tight glucose control by intravenous insulin leading to significantly reduced mortality (14). Of note, in this single-center study mostly surgical ICU patients were investigated and in NICE-SUGAR, a large, randomized, multi-center trial demonstrated increased mortality for intensive glucose control (81 to 109 mg/dL) compared to conventional glucose control (15). Furthermore, in the studies of van den Berghe *et al.* a large amount, namely 87% of the calories were provided via the intravenous route, a practice we do not recommend as it was shown that the mean amount of infused glucose is independently associated with increased acute renal failure, cardiac complications and mortality (16,17). In a summary of five studies (15,18-21) comparing tight glucose control (blood glucose between 80–110 mg/dL) to control groups, an increased risk of death was reported for intensive insulin therapy and the control group showed better survival (OR 0.89; 95% CI: 0.81–0.99; P=0.04) (22). Tight glycemic control was further shown to be associated with brain energy crisis (23). Most probably the "survival benefit" for tight glycemic control reported by van den Berghe *et al.* was due to increased mortality in the control group because of excessive use of intravenous nutrition. For patients with septic shock even a beneficial association between hyperglycemia and mortality was reported by Tiruvoipati *et al.* (3). Accordingly, nowadays hyperglycemia as stress response is thought to be an evolutionary preserved adaptive and beneficial response of the organism (24).

We therefore conclude that (I) further studies investigating the relationship between hypo-perfusion and hyperglycemia are warranted; (II) hyperglycemia is a reliable marker for risk stratification of critically ill patients only in non-diabetics and patients without shock and (III) suggest a permissive and liberal management of high glucose concentrations in those patients which should focus on optimizing tissue perfusion primarily by administering fluids and ensuring proper blood pressure by means of catecholamine-therapy. As hyperglycemia should be considered to be adaptive and beneficial in critically ill septic patients we do not recommend tight glucose control and limit insulin therapy only on avoidance of fluid shifts by hyperglycemic changes of serum osmolality. As parenteral nutrition is associated with excess mortality we recommend using enteral nutrition whenever possible.

Acknowledgements

None.

Footnote

Provenance: This is an invited Commentary commissioned by the Section Editor Zhongheng Zhang (Department of Critical Care Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, Jinhua, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: van Vught LA, Wiewel MA, Klein Klouwenberg PM, *et al*. Admission Hyperglycemia in Critically Ill Sepsis Patients: Association With Outcome and Host Response. Crit Care Med 2016;44:1338-46.

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Cite this article as: Wernly B, Lichtenauer M, Hoppe UC, Jung C. Hyperglycemia in septic patients: an essential stress survival response in all, a robust marker for risk stratification in some, to be messed with in none. J Thorac Dis 2016;8(7):E621-E624. doi: 10.21037/jtd.2016.05.24

