Stress-induced hyperglycemia is a valuable biomarker in febrile neutropenia

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Stress-induced hyperglycemia (SIH) is a transient condition that occurs in patients with acute diseases such as trauma, stroke, surgery and sepsis. Claude Bernard, the eminent French physiologist, described for the first time in 1855 that critically-ill patients tended to show hyperglycemia[1]. In the beginning, it was supposed to be an ancient and adaptive response of tissues requiring large amounts of energy. But by the late 60s, it became clear that SIH was exceedingly frequent in critically-ill patients, and that negative outcomes were generally associated[2]. Since then, there has been a growing interest among clinicians on SIH, although its contribution to risk stratification and therapeutic management remains controversial. More recently, SIH has been described as a significant predictor of poor prognosis in cancer patients with febrile neutropenia (FN).

In this issue, Matias et al. have shed some light on the meaning of SIH in patients with FN in the scenario of induction chemotherapy for acute leukemia[3]. This is indeed a high-risk clinical setting in which the expected rate of infectious-related complications and death has been reported to be around 15%[4]; hence, it is crucial to identify the groups at highest risk for developing life-threatening events in order to design preventive interventions. This is precisely the medical environment in which acute phase biomarkers are especially attractive, since the ineffectiveness of the inflammatory response sets hurdles for assessing the severity of most of the neutropenic infections[5]. In contrast, sources of infection are immediately obvious in non-neutropenic patients and clinical variables are sufficiently informative in these cases.

In agreement with previous reports, Matias et al. found that whereas the prevalence of diabetes is relatively low (5.8%) in this high-risk population, SIH is commonly observed (67.1%) during induction chemotherapy[3]. Moreover, SIH, not diabetic hyperglycemia, was associated with unfavorable outcomes during the course of FN. In fact, after adjusting for comorbidities and other well-known variables, the independent risk factors for severe complications were bacteremia, hypoglycemia and SIH. These data are encouraging for further research to validate the role of SIH as a prognostic marker in large prospective studies. If confirmed, SIH would finally become a valuable, inexpensive and 'easy-to-get' tool in daily clinical practice that could contribute to improve the algorithms of supportive care in the setting of acute leukemia[6].

Although sophisticated biomarkers, such as sTREM-1 and PTX3 are being tested as diagnostic tools in the field of FN, SIH could still play an important role, and some recent discoveries on the molecular basis that underlies the development of sepsis may provide an explanation. Thus, the new depiction conceives SIH as the harbinger of a very ancient and integrative program associated with physiological stress[7]. Counter-regulatory hormones and a milieu of pro-inflammatory mediators play a pivotal role in impairing glucose homeostasis and inducing insulin resistance during sepsis.

But to understand the biological meaning of these metabolic alterations, we should go back to 1925 when Otto Warburg discovered that cancer cells obtained a selective advantage by means of shifting from mitochondrial oxidative phosphorylation to the less efficient anaerobic glycolysis[8]. Since the latter process provides a greater source of intermediates for biosynthesis, the "Warburg effect" can be viewed as the result of the trade-off between the energetic and the plastic needs of cancer cells to sustain rapid proliferation. Wen et al. have suggested similar mechanisms for the inflammatory response that even Otto Warburg apparently missed (Figure 1). Pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharides (LPS) are able to provoke insulin resistance in the liver and smooth muscle, contributing to SIH, and thereby sparing and diverting glucose to monocytes and other immune cells involved in the inflammatory response. At the same time, sepsis induces profound metabolic changes in these immune cells, including a switch to anaerobic glycolysis, resembling the "Warburg effect"[9]. It is possible that the biological meaning of SIH could precisely involve a fine-tuning of their metabolic routes, to obtain a maximum performance during sepsis, while limiting the rise of reactive oxidative species coming from the stressed mitochondria. An early adaptive response is feasible at the beginning of infection[10], and astonishing as it might be, glucose itself behaves

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Table 1 - The relationship between stress-induced hyperglycemia and clinical outcomes in immunosuppressed cancer patients

Author	Clinical setting	n	Clinical outcome according to SIH
Matias et al.[3]	Adult AL	280	SIH was associated to life-threatening complications and infection-related mortality.
Roberson et al.[19]	Childhood ALL	871	There were not significant differences in CR rate, EFS or OS.
Sonabend et al.[20]	Childhood ALL	135	Patients with SIH were more likely to be admitted for FN, and suffered more documented infections.
Derr et al.[21]	Adult BMT	382	SIH was associated to infections and bacteremia. No differences in hospital stay or mortality were reported.
Weiser et al.[22]	Adults ALL	278	Shorter CR duration and median survival is reported. Sepsis and complicated infections were more likely in patients with SIH.
Soysal et al.[23]	FN	86	Patients with SIH had higher mortality. Gram negative and fungal infections were more frequent.
Carmona-Bayonas et al.[13]	FN	175	SIH was an independent predictor of life-threatening complications in apparently stable patients.
Ali et al.[6]	Adult AML	289	SIH is associated to increased hospital mortality.
Fuji et al.[24]	Adult BMT	112	Increased risk of organ dysfunction, GVHD and NRM.

SIH: stress-induced hyperglycemia; AL: acute leukemia; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CR: complete remission; EFS: event-free survival; OS: overall survival; FN: febrile neutropenia; BMT: bone marrow transplantation; GVHD: graft versus host disease; NMR: non-relapse mortality

as a pro-inflammatory molecule[11]. In the late phase of sepsis, this physiological program could turn into a deleterious feedback loop with higher releases of pro-inflammatory molecules and a stronger response to LPS[12]. Thus, SIH might be considered as a compound biomarker indicating both the presence of sepsis and its progression.

In the field of FN, there is already some clinical support to sustain this biological scenario. In a recent report, we analyzed 692 cancer patients with FN and apparent clinical stability at the onset of infection. We developed a prediction model for sepsis-related complications combining an expression of the individual vulnerability (chronic diseases and the performance status), severe mucositis and two biological parameters: precisely monocytopenia and SIH[13]. The prevalence of SIH among patients with neutropenic infections is elevated (16-67%), and it predicts unfavorable outcomes as shown in Table 1. However, the majority of these reports are retrospective and small-sized, so the clinical associations are, at best, hypothesis-generating. Variability in the design and the definition of SIH in each study does not allow drawing definitive conclusions, but are encouraging for further research to validate the role of SIH as a prognostic marker in large prospective studies. Interestingly, these results are also consistent with previous research in the non-cancer population. SIH is one of the major physiological changes in non-neutropenic patients with sepsis, in which it might represent a useful tool for prognostic evaluation and diagnosis of site-specific infections[14]. Moreover, SIH is an independent predictor of adverse outcome, in a pleiad of diseases and clinical settings, such as trauma[15], surgery[16], brain injuries[17], stroke and myocardial infarction.

In summary, it is said that: "There is nothing new under the sun but there are lots of old things we do not know"[18]. SIH is probably one of those integrative "old concepts" that is now being revisited with increasing interest in the field of acute diseases. A new piece in this puzzle is provided by Matias et al. in the specific setting of acute leukemia induction treatment[3]. Future prospects may transform this easily available information into new approaches to stratify and treat neutropenic infections.

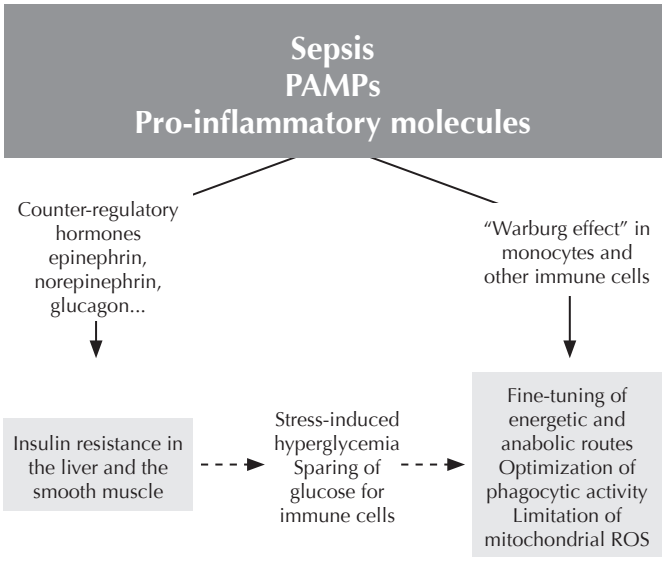

Figure 1 - A plausible framework to understand SIH. SIH can be involved in an early adaptive response to sepsis. In more advanced phases, the exhaustion of the immune system leads to a deleterious feedback loop, with increasing pro-inflammatory mediators, and sepsis progression. (Adapted from: Wen H et al.[9])

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