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Revisión

"Glycemic variability": a new therapeutic challenge in diabetes and the critical care setting

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Abstract
Much attention is recently paid to the possibility that oscillating glucose may superimpose to HbA_{1c} levels in determining the risk for diabetic complications. Furthermore, recent evidences suggest glucose variability as worsening factor for the prognosis in the acute care settings. In vitro and in animal studies confirm that oscillating glucose is more dangerous that stable constant high glucose, particularly in activating the pathways involved in the pathogenesis of diabetic complications. The production of free radicals, accompanied by an insufficient increase of the intracellular antioxidant defenses seem to account for this phenomenon. Human studies also confirm that fluctuating glucose produces an increase of free radicals as well as endothelial dysfunction which are worse that those produced by stable high glucose. Avoiding glucose fluctuations in diabetic patients seems to be an emerging challenge in the treatment of diabetes.

Keywords: glucose variability, diabetic complications, acute care settings, oxidative stress.

Introduction
In both type 1 and type 2 diabetes, large prospective clinical studies have shown a strong relationship between time-averaged mean levels of glycemia as measured by haemoglobin A_{1c} (HbA_{1c}) and diabetic complications.[1-3] However, in recent years, several pieces of evidence have raised the possibility that glycemic instability may contribute, perhaps more than HbA_{1c} levels, to the development of diabetic complications.[4]

First, the observation that both in diabetic patients and in people with impaired glucose tolerance (IGT), the glycemic value of the glycemia two hours after glucose challenge is a stronger predictor of cardiovascular disease than is fasting glycemia.[5] Second, the finding that increased postprandial glycemia can have the same deleterious effect on the appearance of cardiovascular disease.[5] The third and final piece of evidence has been that the presence of acute hyperglycemia during an acute MI[6] or in patients in the critical care setting[7] can lead to a worse prognosis, both in diabetic and non diabetics. Further, these findings have been supported pathophysiologically, by evidence that an acute increase of glycemia can produce significant alterations in normal homeostasis, such as endothelial dysfunction and inflammation.[6] Taken together, these data begin to explain the role of an acute increase of glycemia in the development of cardiovascular disease or in worsening the prognosis of acutely ill patients.

However, the concept of glucose variability, even taking the above evidences into the consideration, is a more complex phenomenon, because it introduces the idea that multiple fluctuations of the glycemia in the same individual could be more dangerous than chronic stable hyperglycemia or a simple episode of acute hyperglycemia.

Clinical evidences in diabetes
Recent studies with continuous glucose sensors found a large range of glucose values in children with type 1 diabetes, even in those with excellent HbA_{1c} values, which raises the possibility that in addition to HbA_{1c}, glucose variability may have predictive value for the development of diabetic complications.[8] An extensive evaluation of this concept has been done by Kilpatrick et al.,[9] who first reported that glycemic instability is not a predictor of microvascular complications in patients from the DCCT, in particular retinopathy,[9] and then reported that mean daily glucose as well as pre and postprandial hyperglycemia are predictors for cardiovascular disease in the same cohort.[10] Interestingly, the same author more recently reported that HbA_{1c} instability is a predictor of microvascular complications in the same patient cohort.[11] Although the methodology of these studies, particularly of the first,[12] has been largely criticized,[13] these papers show that the instability of some indexes of glycemic control might be deleterious for complications in type 1 diabetes.

A recent study[14] followed type 1 diabetic patients over an 11-year period. Onset and progression of micro- and macrovascular complications were recorded and as expected, these increased over time. The standard deviation of blood glucose (SDBG) (i.e., glucose variability) concentration was calculated from 70 self-monitored measurements taken over a period of four weeks. Statistical analyses showed that HbA_{1c} was an independent predictor of the incidence and prevalence of nephropathy. SDBG was found to be a predictor of the prevalence of peripheral neuropathy, and a highly significant predictor of hypoglycemic unawareness. These data suggest that glucose variability may be important in the development of peripheral neuropathy in patients with type 1 diabetes, and that the nervous system may be particularly vulnerable to glycemic variability.[14]

In type 2 diabetes the data are less consistent. Several years ago Muggeo et al. found in elderly diabetic patients that mortality from all causes[12] and from cardiovascular disease[15] was main-

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ly related to the variability/instability of fasting glycemia rather than to its absolute values. Further evidence is that in people with impaired glucose tolerance (IGT) the glucose "spike", i.e. the absolute difference between the basal glycemia and the peak glycemia during the glucose challenge, is a strong predictor of intima-media thickness (IMT), a marker of endothelial dysfunction.[16] Another study drew similar conclusions in type 2 diabetic patients, but this time the glucose "spike" was defined as the absolute difference between the pre-meal and peak glycemia during the meal.[17]

Clinical evidence in Critical Care Settings

Not surprisingly, the above evidence is of great interest to the diabetes community. Additional studies, however, strongly suggest that glucose variability is playing a critical role as an independent risk factor in worsening the prognosis of a number of other clinical settings.

Recent studies revealed a significant association between hyperglycemia and increased morbidity and mortality rates among adult patients, both diabetic and non diabetic, in the ICU.[7] However, in a first seminal study, there were over 168,000 blood glucose measurements in a study cohort of seven thousand critically ill patients.[18]The SDBG concentration was found to be statistically higher in non-survivors as compared to survivors. Further, SDBG was significantly associated with intensive care unit and hospital mortality, showing that the variability of blood glucose concentration is a significant independent predictor of intensive care unit and hospital mortality.[18] These data have recently been confirmed in a retrospective review of a large cohort of prospectively evaluated patients.[19] Three thousand two hundred fifty-two patients consecutively admitted between October 1999 and October 2007 with at least three venous glucose samples were evaluated. A significant increase in mortality in this study was observed in hyperglycemic as compared to normoglycemic patients. Further, the relationship between glycemic variability and mortality was strongest in the euglycemic range. For patients with mean glucose level 70 mg/dL to 99 mg/dL, mortality ranged from 6% in patients with low glycemic variability to 30% with patients with high glycemic variability. For patients with mean glucose levels of 100 mg/dL to 119 mg/dL, the corresponding change was from 9.7% in low variability to 31.0% in high variability. Mortality among patients in the entire cohort low (first quartile) of glycemic variability was 12.1%, increasing to 19.9%, 27.7%, and 37.8% in the second, third, and fourth quartiles. Intensive care unit length of stay was statistically shorter among patients in the first quartile compared with those in the other three quartiles. This study, therefore, demonstrated that increasing glycemic variability conferred a strong independent risk of mortality in this heterogeneous population of critically ill patients.[19]

Similar results are available in the Pediatric ICU (PICU). Hyperglycemia has been found to be an important negative prognostic factor and an indication of poor neurological long-term outcomes among pediatric patients with traumatic head injuries.[20] Among infants diagnosed as having necrotizing enterocolitis, hyperglycemia is common and is associated with longer lengths of stay and increased rates of late death in the Neonatal ICU.[21] Srinivasan et al.[22] focused on a subgroup of severely ill pediatric patients receiving vasoactive infusions or mechanical ventilation. Those authors reported that peak blood glucose levels and duration of hyperglycemia were associated independently with PICU mortality rates. Recently, Faustino and Apkon[23] examined the prevalence of hyperglycemia among 942 non-diabetic critically ill children and found a correlation between the relative risk of dying and hyperglycemia.

In a recent study,[24] medical records at the Packard Children's Hospital at Stanford University were reviewed retrospectively for all non-diabetic PICU admissions for a one-year period. From 1,094 eligible admissions and 18,865 glucose values, it was first found that hyperglycemia was prevalent, with 86% of patients having blood glucose levels over 120 mg/dL. Further, patients with mean glucose levels over 200 mg/dL had a significantly longer median PICU length of stay and mortality as compared to patients with glucose levels <110 mg/dL. Hypoglycemia was also prevalent and it was found that minimal glucose levels of <65 mg/dL resulted in both increased length of PICU stay (9.5 days vs 1 day) and patient mortality rate as compared to patients with blood glucose levels <110 mg/dL. Additionally, glucose variability, taken to be periods of both hyperglycemia and hypoglycemia, showed the strongest association with mortality rates and an association with PICU length of stay. This was also the conclusion of another PICU study.[25] Non-diabetic children admitted to a PICU for >24 hrs with at least one blood glucose level recorded from a 1 year period were examined. Patients were categorized as having isolated hyperglycemia (blood glucose ≥150 mg/dL), isolated hypoglycemia (blood glucose ≤60 mg/dL), and glucose variability (both hyper- and hypoglycemia). Hyperglycemic, hypoglycemic, and glucose variability measurements occurred in 56%, 10% and 7% of all patients, respectively. Glucose variability and hyperglycemia were significantly associated with increased patient mortality. There were no deaths among patients with isolated hypoglycemia. Hyperglycemia and glucose variability were also associated with nosocomial infections and increased hospital length of stay. Another recent paper[26] confirmed that glucose variability is independently associated with hospital mortality in patients with nosocomial infections.

From the above studies it seems clearly emerging that glucose variability could be harmful not only for diabetic patients but for those patients in critical care settings.

Laboratory evidence

Several laboratory studies have already approached the issue of the "glucose variability".

A deleterious effect of glucose fluctuations on renal mesangial,[27]renal tubulointerstitial,[28] umbilical endothelial[29] and pancreatic beta cells[30] has been reported. Specifically, mesangial[27] and tubulointerstitial[28] cells cultured in periodic high glucose concentration increase matrix production more than cells cultured in high stable glucose concentrations. Increased apoptotic cell death was observed in both beta[30] and endothelial[29] cells in response to fluctuating as compared to continuous high glucose concentrations. Interestingly, in human renal cortical fibroblasts[31] it has been shown that the increased expression of fibrogenesis markers is dependent on high glucose "peaks" but is independent of total amount of glucose to which cells are exposed.

Oxidative stress, in particular the increased superoxide production at the mitochondrial level, has been suggested as the key link between hyperglycemia and diabetic complications.[32] Evidence suggest that the same phenomenon underlines the deleterious effect of oscillating glucose, leading to a more enhanced deleterious effect of fluctuating glucose compared to constant high glucose.[33-36]

Experiments in animals also support the hypothesis of a deleterious effect of fluctuating glucose. Recently, Azuma et al.[37] have established a method which allows for the observation of the entire surface of the endothelium of a rat aorta to count the number of attached monocytes, a marker of vascular inflammation.[37] Using this method, these authors have demonstrated that repetitive fluctuation of hyperglycemia resulted in significantly induced monocyte-endothelial adhesion as compared to sustained hyperglycemia.[38] Furthermore, to assess the role of glucose fluctuations on atherogenesis, they used atherogenic-prone mice fed maltose twice daily to model of repetitive glucose spikes.[39] The results show that fluctuations in blood glucose concentrations accelerated macrophage adhesion to endothelial cells and the formation of fibrotic arteriosclerotic lesions. The same group was also able to show that reducing glucose "swings" is accompanied by a significant decrease of monocyte-endothelial adhesion.[40,41]

All the above laboratory data are consistent with clinical data. Specifically, repeated fluctuations of glucose produce increased circulating levels of inflammatory cytokines as compared to stable high glucose in normal subjects, as well as endothelial dysfunction in both normal and type 2 diabetic patients.[42] The role of oxidative stress also seems to be a key causative factor clinically, since the use of an antioxidant reduced the phenomenon in both the studies.[42] Consistent with the hypothesis of an involvement of oxidative stress is the evidence that in type 2 diabetes daily glucose fluctuations are strongly predictive of increased generation of an oxidative stress.[43] However, the same result has not been confirmed in type 1 diabetes.[44]

Even if oxidative stress generation appears to be the key player of all the phenomena reported above, the precise mechanism through which oscillating glucose may be worse than constant high glucose, remains not completely defined. Although further studies are certainly warranted, these would be quite difficult to accomplish in humans. A possible explanation is that in oscillating glucose conditions the cells are not able sufficiently to increase their own intracellular antioxidant defenses,[45] a condition which has been suggested to favor the development of diabetic complications.[46,47] In this regard, a recent study showed that during acute hyperglycemia, in normal subjects, several genes involved in free radical detoxification were down-regulated.[48]

Conclusions

Accumulating evidence suggests that glucose "variability" in terms of widely glucose fluctuations may have a deleterious effect in worsening the prognosis not only for diabetic complications but also for several critical care situations. The hypothesis that maintaining the level of glycemia under very strict control would be relevant in any clinical setting is, in our opinion, stressed by the recent evidence that in normal people glycemia maintained in very narrow range of 70-140 mg/dL.[49] One can argue that if the human body spends so much energy to maintain the blood glucose level under a so strict a range, it is because otherwise it could be deleterious. Indeed, the studies presented in this review suggest that this is the case. While waiting for more detailed and ad hoc designed studies, particularly intervention studies, now is the time to raise attention on this new therapeutic challenge not only of diabetes but also of a number of critical conditions. ■

Potential conflicts of interest

None.

Key messages

- Glucose variability is an emerging risk factor for diabetic complications.
- Glucose variability worsens the prognosis in the acute care settings.
- Oxidative stress seems to be the mediator of the deleterious effects of glucose variability.

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