



Tight Glucose Control in Sepsis

Dr. Pedro Celiny Ramos Garcia

UTI Pediátrica – Hospital São Lucas - Faculdade de Medicina Pontifícia Universidade Católica do RS - Brasil



Celiny@terra.com.br

1

Porto Alegre, Brasil





Sorry for my mistakes and this "Brazilian" English

It is because of my Portuguese!





Introdution

Stress-hyperglycemia and insulin resistance

✓ Are very common in PICU patients mainy in those with sepsis Multiple pathogenetic mechanisms

are responsible for this metabolic syndrome

 Increased pro-inflammatory mediators and counter-regulatory hormones may play a critical role





Introdution

Attempts to modulate the inflammatory response

 ✓ using specific inflammatory mediators have failed to improve outcome in critical care

More recently, however, some data suggest

Tight glycemic control with insulin

 ✓ May restore the balance between pro-inflammatory and anti-inflammatory mediators and improve the outcome of critically ill patients

van den Berghe G et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001

van den Berghe G et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. Crit Care Med 2003



Background

More than one hundred years ago...

1878 - Claude Bernard

Postulated that...

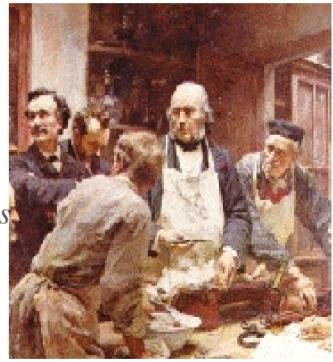
✓ Systems respond to pathogens by maintaining cellular homeostasis

1914 - Cannon

✓ Showed that disturbs to this homeostasis induce a response from the organism

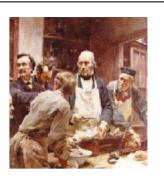
1936 - Hans Selye

✓ Explained this mechanism using the General Adaptation syndrome or "stress"





Concept of glycemic control is in line with this historical physiological principles

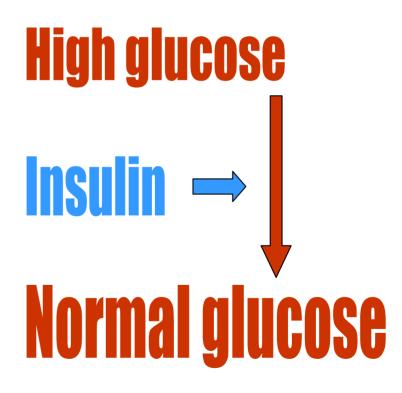


Refurns a deranged variable

using a hormone normally produced by the organism

To its normal status





Celiny@terra.com.br



"Diabetes of Stress"

The mechanism of stress induced hyperglycemia is well studied.

In situations of stress, such as sepsis

- There is an increment in counter-regulatory hormones (most important Cortisol)
- ✓ *Release of cytokines and catecholamines.*

This response induce an insulin resistance state

✓ That sustain hepatic glyconeogenesis
✓ And impair peripheral glucose uptake.

These changes will reflect, clinically, in hyperglycaemia

This glucose nivel up to 200mg/dL

✓ *Historically have been tolerated*

Because it was considered part of an adaptive stress response



Hyperglycemia in the ICU

In the last decade, this concept started to change

Retrospective studies in critically ill adults, showed that hyperglycemia was very frequent

- ✓ That hyperglycemia at the time of admission or soon after was associated with poor outcome
- ✓ The association of high glucose level with poor outcome was evident not only in diabetics, but also in non-diabetic patients

Norhammar AM et al. Admission plasma glucose: independent risk factor for long-term prognosis after myocardial infarction even in nondiabetic patients. Diabetes Care 1999.

Laird AM et al. Relationship of early hyperglycemia to mortality in trauma patients. J Trauma 2004.

Capes SE et al. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 2000



Hypergly cemia in the ICU

More recently

Prospective studies in adults concluded that hyperglycemia resulted in worse outcome

 ✓ Patients with high glucose had longer intensive care and hospital stay, higher secondary infection rates, and higher mortality.

However, these associations do not necessarily reflect causation

Sung J et al. Admission hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma 2005

Lazar HL et al. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. Circulation 2004

Ingels C et al. Strict blood glucose control with insulin during intensive care after cardiac surgery. Eur Heart J 2006



In 2001, van den Berghe published

A randomized controlled trial of tight glycemic control in a surgical intensive care unit.

- ✓ Patients who received insulin and maintain Glucose levels between 80 -110 m/dl
- ✓ Had a 42% relative reduction in mortality.
- ✓ Insulin therapy also reduced several intensive care morbidities

Such as renal failure and secondary sepsis

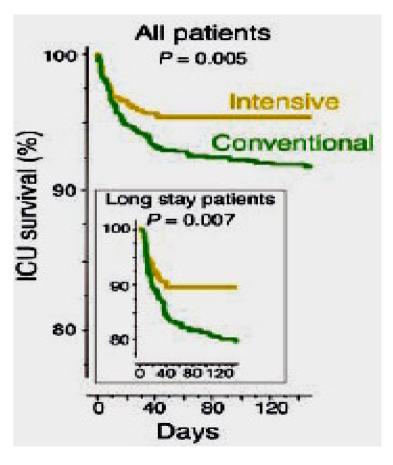
The main concerns to extrapolate the results of this study were

- ✓ That it was a adult surgical ICU
- ✓ Feeding protocol used large caloric intake,
- \checkmark High mortality in the control group

Despite these problems, this study had a big repercussion around the world, and insulin therapy was adapted as a standard treatment in several adult ICUs (and pediatrics).



Van den Bergue et al. Intensive insulin therapy in the critically ill patients. N Engl J Med, 2001



In 2006, the van den Berghe group published

Randomized controlled trial of insulin therapy in a medical critical care.

- ✓ The role of glycemic control in the medical ICU to decreasing mortality was not shown
- ✓ Insulin reduced renal failure and reduced length of ICU stay,

But did not change the incidence of sepsis

Among patients who stayed in ICU for more than 3 days

 ✓ Insulin therapy reduced ICU mortality (38% vs 31%) and morbidity.

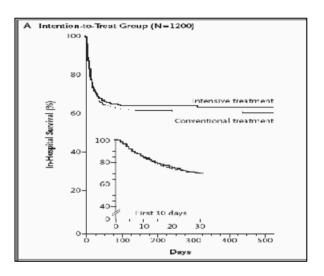
Concerns with this study,

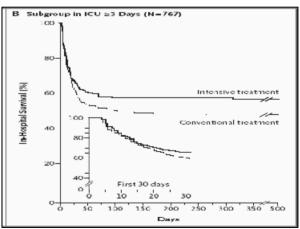
 Again, was the feeding protocol and a relatively high mortality in control group

Also, the incidence of hypoglycaemia was very high (18.7%) and hypoglycaemia was an independent risk factor for mortality.



Van den Berghe G et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006

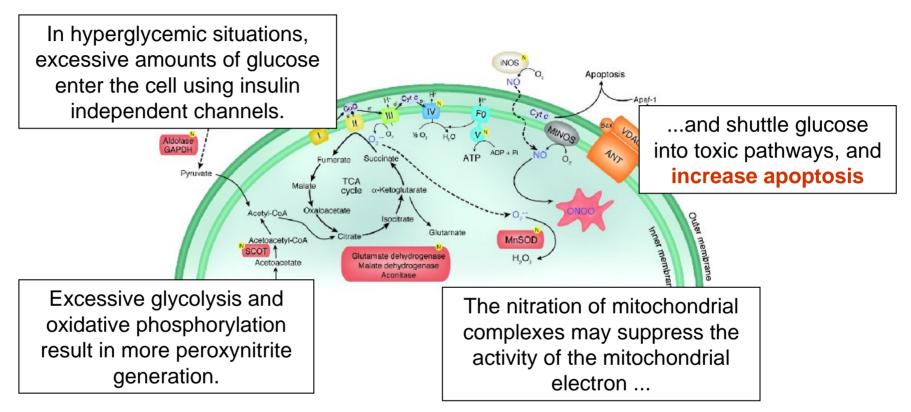




Leuven Study Medical (2006)

Celiny@terra.com.br

Mechanism of Glucose Toxicity



- ✓ Despite the evident effects of insulin therapy in critical illness, it is still not clear which is the main mechanism involved.
- ✓ Glucose toxicity mechanisms, well known from diabetes models, can explain some of these effects



Van den Berghe, G. J. Clin. Invest. 2004



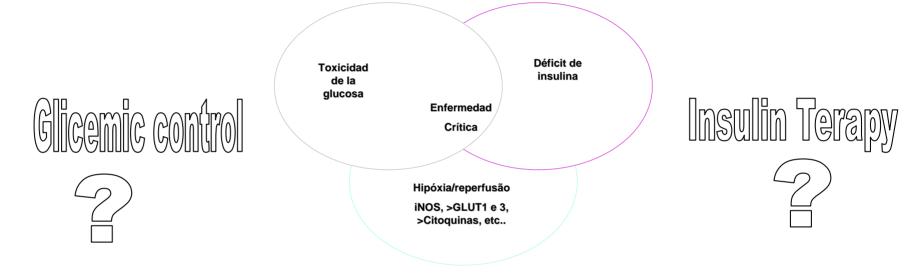
On top of the possible benefits from reducing glucose toxicity Insulin itself may have beneficial effects

- ✓ Has Anti-inflammatory effects
 Suppresses nuclear factor kB (NFkB)
 Inhibit interleukyne production
- ✓ Improve of dyslipidemia
- ✓ Reduces endothelial dysfunction and hypercoagulation
 ✓ Suppresses nitric oxide



With possible benefical effects of both glycose control and insulin, it is not clear which is the mechanis that improved outcome in insulin therapy studies.

Mixed Insulin and Normogly cemia beneficial effects



✓ Some evidence that normoglycaemia plays the major role in the benefits, but it is likely that both effects contributed to the benefits found..

Ellger B et al. Survival benefits of intensive insulin therapy in critical illness: impact of maintaining normoglycemia versus glycemia-independent actions of insulin. Diabetes 2006

Van den Berghe et al. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. CCM 2003



15

Stress hyperglycemia in Pediatrics

In children, for a long period, little or no attention was given to hyperglycemia in critically ill children

- ✓ Case reports in the early 90s have reported hyperglycemia in pediatrics
 - Rabinowitz L et al. Arch Dis Child 1984
 - Chernow B et al. Crit Care Med 1982
 - Ronan A et al. J Pediatr 1997
- ✓ Stress hyperglycemia' was suggested to be associated with the eventual development of type 1 diabetes.
 - Vardi et al. J Pediatr 1990
 - Shehadeh N et al. J Pediatr Endocrinol Metab 1997



Prevalence of Stress hyperglycemia

One of the first attempts to study the prevalence and associations of hyperglycemia in non diabetic children was performed in 94.

This study evaluated more than nine hundred children (926) visiting an emergency department

✓ Near four % (3.8) of these children had glucose above 150mg/dL.

- ✓ Risk factors were high fever, admission, and intravenous fluids
- \checkmark The sickest children were the children with the highest glucose

Bhisitkul DM et al. Prevalence of stress hyperglycemia among patients attending a pediatric emergency department J Pediatr 1994



Stress hyperglycemia and mortality

The first study to associate 'stress hyperglycemia' with mortality

Study from India, published in 97 with up to sevem hundred (758) children with acute illness

- ✓ This study showed a prevalence of hyperglycemia (150 mg/dl) near five % (4.7%) in acute illness
- ✓ Mortality in the hyperglycemic group was double but not statistically significant.
- ✓ Conclude that hyperglycemia was common, transient and not clinically significant.

Gupta P et al. Transient hyperglycemia in acute childhood illnesses: to attend or ignore? Indian J Pediatr 1997



More recently, a number of studies evaluated the association of hyperglycemia with poorer outcome.

In traumatic brain injury in children

✓ Admission glucose above 300 and serum glucose levels were associated with higher mortality

Chiaretti A et al. Childs Nerv Syst 1998 - Cochran A et al. J Trauma 2003.

In newborns with enterocolitis and parenteral nutrition

 ✓ Hyperglycemia was also associated with poorer outcome Hall NJ et al. J Pediatr Surg 2004 - Alaedeen DI et al. J Pediatr Surg 2006

In critically ill children the first retrospective study

- ✓ In this study blood glucose level above 126 mg/dL was noticed in 86% of the patients
- ✓ Peak glucose and duration of hyperglycemia were independently associated with PICU mortality.

Srinivasan V et al. Pediatr Crit Care Med 2004



Faustino EV, Apkon M. Persistent hyperglycemia in critically ill children. J Pediatr 2005

In a retrospective study with up to 900 postoperative cardiac infants relating initial, peak and duration of hyperglycemia to outcome.

- ✓ Initial glucose level did not correlate with risk of death.
- \checkmark A correlation between the risk of dying and glucose over 150 mg/dl
- ✓ Maximum glucose within 24 h and within 10 days correlated with inhospital mortality and longer LOS

Cutoff value	Mortality rate above cutoff value	Mortality rate at or below cutoff value	Relative risk (95% Cl)
Initial glucose			
120 mg/dL	24/582 (4.1 %)	12/360 (3.3 %)	1.24 (0.63, 2.44)
150 mg/dL	13/345 (3.8 %)	23/597 (3.9 %)	0.98 (0.50, 1.91)
200 mg/dL	7/157 (4.5 %)	29/785 (3.7 %)	1.21 (0.54, 2.71)
Maximum glucose within 24 h of initial glucose	. ,		
120 mg/dL	30/663 (4.5 %)	6/279 (2.2 %)	2.10 (0.89, 5.00)
150 mg/dL	24/419 (5.7 %)	12/523 (2.3 %)	2.50 (1.26, 4.93)
200 mg/dL	14/210 (6.7 %)	22/732 (3.0 %)	2.22 (1.16, 4.26)
1aximum glucose within 10 d of initial glucose	. ,		
120 mg/dL	34/706 (4.8 %)	2/236 (0.8 %)	5.68 (1.38, 23.47)
150 mg/dL	29/472 (6.1 %)	7/470 (1.5 %)	4.13 (1.83, 9.32)
200 mg/dL	20/248 (8.1%)	16/694 (2.3%)	3.50 (1.84, 6.64)

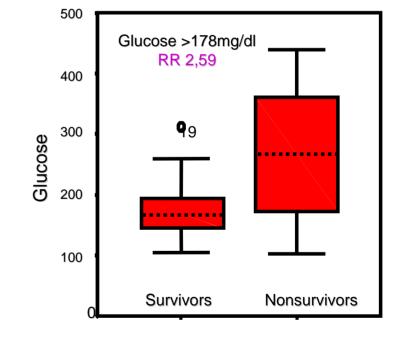


Branco RG, Gacia PC, Piva JP et al. Glucose level and risk of mortality in pediatric septic shock. Pediatr Crit Care Med 2005

We performed in 2005 a prospective observational study evaluating glucose levels in children with septic shock

- ✓ We study 57 children with septic shock refractory to volume
- ✓ The peak glucose value was determined and severity of illness was measured by PRISM score
- ✓ Medications, corticosteroids, caloric intake, and infusions, were recorded.
- ✓ The peak glucose was higher in nonsurvivors (262 vs 167 mg/dl)

A peak glucose level of over 178 mg/dl was associated with a 2.5 fold increased risk of death







Wintergerst KA et al. Association of hypo, hyperglycemia, and glucose variability with morbidity and death in the PICU. Pediatrics 2006

A series of other studies have now reported that hyperglycemia is associated with poorer outcome. Interestingly, hypoglycemia is poorly studied

Retrospective study, with more than one thousand children

✓ Hypoglycemia, hyperglycemia and glucose variability were associated with increased LOS and mortality

\checkmark So, hypoglycemia can be as dangerous as hyperglycemia

Glucose Cutoff, ^a mg/dL	No.	PICU LOS, Median (IQR), d	Total LOS, Median (IQR), d	Deaths According to Quintile, <i>n</i> (%)
>65	798	2 (1–5) ^h	7 (4–14) ^t *	20 (2.5) ^b
<110	130	1 (1-2) ^b	5 (3-9) ^{ts}	2 (1.5)°
>110	850	4 (2–8) ^h	9 (5–19) ⁿ	48 (5.7) ^s
<150	382	2 (1-3) ^h	6 (3-12) ^b	6 (1.6) ^b
<200	635	2 (1-4) ^h	7 (4-13)**	16 (2.5) ^b
>200	345	6 (3-13) ⁿ	14 (6-32) ¹¹	34 (9.9) ^b

Hospital LOS and Mortality Rates According to Glucose Cutoff Values

Analysis was performed with Pearson's χ^2 calculation.

van Waardenburg DA, et al. Hyperglycemia in children with meningococcal sepsis and septic shock: the relation between plasma levels of insulin and inflammatory mediators. J Clin Endocrinol Metab 2006

Observational cohort study

- ✓ Comparing children with meningococcal sepsis with meningococcal septic shock (MSS)
- ✓ Maximum glucose levels were higher in shock patients than in sepsis patients and correlated with severity of illness

Insulin levels in shock patients were significantly lower (7.2 vs 19.0mU/I)

 ✓ Some illness states in children with hyperglycemia are marked by hypoinsulinemia, rather than hyperinsulinemia associated with insulin resistance.

This is in contrast to the classical description of insulin resistance with normal or high levels of insulin.



Pham TN et al. Impact of tight glycemic control in severely burned children. J Trauma. 2005

Retrospective review

✓ 64 severely burned children- 24 insulin
Intensive Insulin Therapy vs Convencional
✓ >140mg/dL (goal 90-120) vs >200 mg/dL(goal<200)
✓ More intensive insulin studies inclusion 17/33 vs 7/31
✓ More duration of insulin therapy ~9 to 38 days
✓ Less Insulin dose (IU/kg/d) ~ 2 to ~4
✓ Less mortality in the most burned (>50%)
✓ Less LOS ? Less sepsis? Infection ? NS

More hypoglycemic episodes 9 (53%) vs zero (0%)





Should we start using insulin in critically ill children?



It is tempting but we need to have more evidence...



Lack of Pediatric Evidence

First, there is no randomized controlled trial evaluating use of insulin in critically ill Children



Kleina GW et al. Hyperglycemia in the PICU. Curr Opin Clin Nutr Metab Care 2007



Lack of Pediatric Evidence



Second, most studies are retrospective

✓ And they can introduce biases

- For example, sicker patients need more monitoring, so they will have more glucose measurement – and more chances to find hyperglycemia
- ✓ More, the association of hyperglycemia with longer PICU stay may be because children who stay longer in PICU may have more opportunities for an elevated glucose level to be identified.

Third, association of high glucose with high mortality does not mean a cause.

✓ It may be that sicker patients have higher glucose only because they are more stressed.

Kleina GW et al. Hyperglycemia in the PICU. Curr Opin Clin Nutr Metab Care 2007

The hypoglycaemia scare

Other big concern of insulin use is the risk of hypoglycemia

✓ Hypoglycemia in children is a risk factor for mortality.

✓ This may be due to deleterious effects of hypoglycemia

✓ Or because these children had hypoglycemia because their counter-regulatory response was insufficient.

In any way, hypoglycemia increases the risk of death

 And use of insulin can induce hypoglycemia
 So use of insulin need to be considered very carefully





The hypoglycaemia scare

More, in the medical Leuven study

✓ ICU stay of less than 3 days had high mortality if they received insulin.

Children have PICU shorter than the average adult ICU stay

- ✓ So children may not have enough time to benefit from insulin.
- ✓ Moreover, acute hyperglycemia is protective in vitro
- ✓ So hyperglycemia for a short period could be beneficial.

Van den Berghe G et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006





Difficulty to implement glucose control

- Cutoffs for hyperglycemia based on adult
 - ✓ 126 mg/dl cutoff for diagnosis of diabetes (fasting state)
 ✓ Such cutoffs are appropriate in children?
- Effects of other drugs in glucose metabolism
 - ✓ Corticosteroid use
 - ✓ Ionotropic use
- Similar problems with adults...but lower doses
 - ✓ High incidence of hypoglycemia
 - ✓ Need for close glucose monitoring
 - ✓ Increase in nursing workload





Should we start using insulin in critically ill children?



Up to now, insulin should no be routinely use in children

Use of insulin in PICU should be very careful

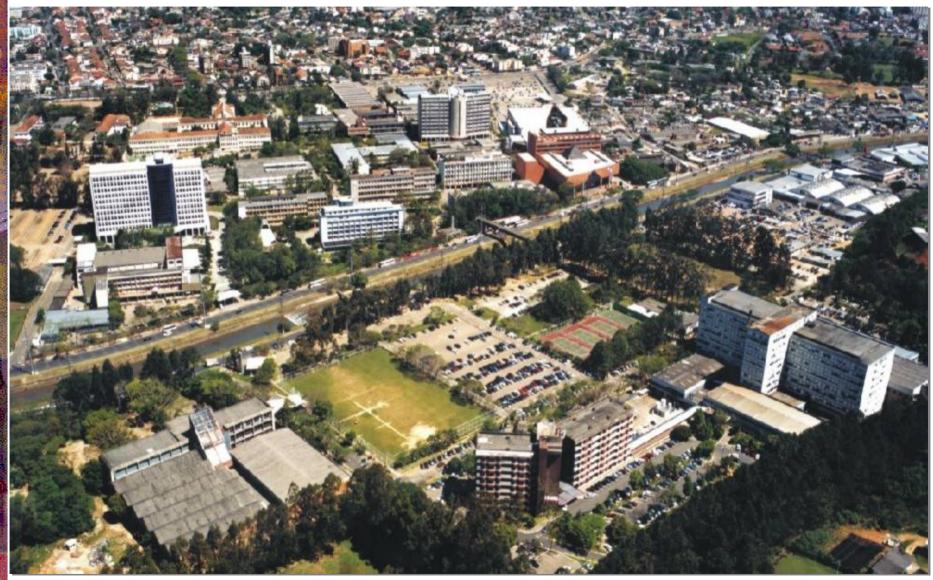
Several studies are being performed to help us to make this decision







PUCRS - Pontifícia Universidade Católica do Rio Grande do Sul





Muito obrigado!



UTI Pediátrica - Hospital São Lucas da PUCRS

Porto Alegre –RS - Brasil



DAY 3: Wednesday, June 27, 2007: Day of Integration

DAY 3 TRACKLINES SEPSIS
12:00 -12:30
Tight Glucose Control in Sepsis

Pedro Celiny Garcia, Brazil

