

Perioperative glycemic control

Ayman A Radi MD*, Nagwa M Doha MD*, Wafiya R Mahdy and Mohamed Hamdin Mandor M.B.B.Ch**

* Department of Anesthesia and Intensive Care Medicine, Faculty of Medicine, Menofya University.

**Nasr city insurance hospital Cairo.

drmohammadhamdinmandor@yahoo.com.

Abstract: Objective: Review perioperative glycemic control. **Data Sources:** medical text books, medical journals, medical websites which have updated researches with key words (glycemic control) in the title of the paper. **Study selection:** Systematic reviews that addressed perioperative glycemic control. **Data Extraction:** Special search was done at midline with key words (glycemic control) in the title of papers; extraction was made, including assessment of quality and validity of papers that met with the prior criteria that describe review. **Data synthesis:** The main result of the review. Each study was reviewed independently; obtained data is rebuilt in new language according to the need of the researcher and arranged in topics through the article. **Recent Findings:** Compared to hyperglycemia due to diabetes, stress induced hyperglycemia is a particular challenge in inpatient care, as its prevalence and natural history are not well defined and its occurrence is unpredictable and often unanticipated by providers. Higher mortality was noted in patients without diabetes requiring insulin compared to patients with known diabetes suggesting that stress hyperglycemia may represent a different pathophysiology and natural history than in patients with known diabetes. Optimization of the patient's preoperative medications and the use of insulin infusions, as well as surgical and anesthetic technique, are important factors for achieving desirable perioperative blood glucose control. Minimizing blood glucose variability during surgery should be part of the glycemic control strategy. Advances in real-time glucose monitoring may benefit hospitalized diabetic and nondiabetic patients. **Conclusions:** Balancing the risks of hypoglycemia against the known benefits in morbidity and mortality is the goal, and, although intensive glycemic control continues to be standard of care, current consensus guidelines recommend less stringent glycemic goals, typically between 80-150 mg/dL.

[Ayman A Radi, Nagwa M Doha, Wafiya R Mahdy and Mohamed Hamdin Mandor. **Perioperative glycemic control.** *J Am Sci* 2014;10(8):262-266]. (ISSN: 1545-1003). <http://www.jofamericanscience.org>. 36

Key words: DM, perioperative hyperglycemia, glycemic control.

1. Introduction:

Perioperative stress hyperglycemia refers to transient elevations in blood glucose that occur during surgery in patients without diabetes, or as an exacerbation of hyperglycemia in subjects with diabetes mellitus that resolves after resolution of the acute illness. ⁽¹⁾

There is two diagnostic categories of stress hyperglycemia—hospital-related hyperglycemia according to the American Diabetes Association (ADA) consensus definition (fasting glucose >6.9 mmol/L (125 mg/dl) or random glucose >11.1 mmol/L(200 mg/dl) without evidence of previous diabetes), and pre-existing diabetes with deterioration of preillness glycemic control. ⁽²⁾ perioperative hyperglycemia is often caused or aggravated by the use of medications such as glucocorticoids, octreotide, vasopressors, and immunosuppressant agent or by the administration of enteral and parenteral nutrition. ⁽³⁾

Perioperative hyperglycemia is associated with longer hospital stay, higher health care resource utilization, and greater perioperative mortality and morbidity. ⁽⁴⁾

2. Materials and Methods

The guidance published by the Centre for Reviews and Dissemination was used to assess the methodology and outcomes of the studies. This review was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement. An institutional review board and ethics committee approved this study.

Search Strategy

A systematic search was performed of several bibliographical databases to identify relevant reports in any language. These included MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, TRIP database, Clinical Trials Registry, ISI Web of Knowledge, and Web of Science. Articles electronically published ahead of print were included. The search was performed in the electronic databases from the start of the database up to 2014.

Study Selection

All the studies were independently assessed for inclusion. They were included if they fulfilled the following criteria:

Participants: perioperative glycemic control

Interventions: Therapeutic modalities including insulin strategies of treating patients with perioperative hyperglycemia.

Outcomes: Improvement prognosis in patients with perioperative hyperglycemia.

If the studies did not fulfill the above criteria, they were excluded. Articles in non-English languages were translated. The article title and abstracts were initially screened and then, the selected articles were read in full and further assessed for eligibility. All references from the eligible articles were reviewed in order to identify additional studies.

Data Extraction

Study quality assessment included whether ethical approval was gained, prospective design, eligibility criteria specified, appropriate controls used, adequate follow-up achieved, and defined outcome measures.

Quality Assessment; the quality of all the studies was assessed. Important factors included, prospective study design, attainment of ethical approval, evidence

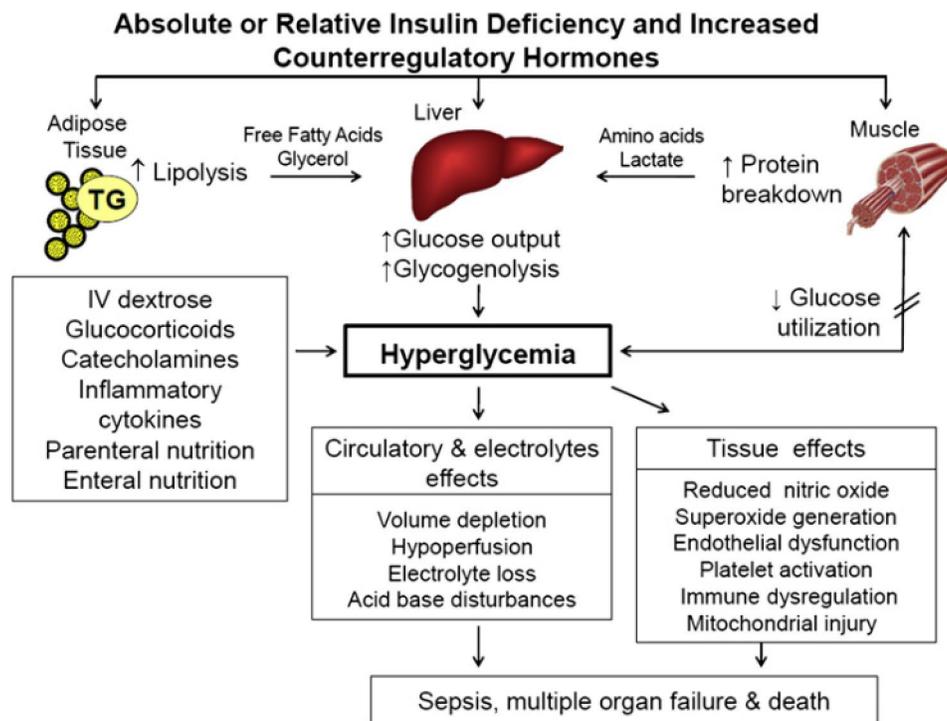
of a power calculation, specified eligibility criteria, appropriate controls, specified outcome measures and adequate follow-up. It was expected that confounding factors would be reported and controlled for and appropriate data analysis made in addition to an explanation of missing data.

Data Synthesis

Because of heterogeneity in postoperative follow-up periods and outcome measures reported, it was not possible to pool the data and perform meta-analysis. Comparisons were made by structured review.

3. Results (finding)

Balancing the risks of hypoglycemia against the known benefits in morbidity and mortality is the goal, and, although intensive glycaemic control continues to be standard of care, current consensus guidelines recommend less stringent glycaemic goals, typically between 80-150 mg/dL.



(Fig. 1): Consequences of stress hyperglycemia in surgical patients. ⁽⁵⁾

4. Discussion

Pathophysiology of Perioperative Hyperglycemia;

Perioperative insulin resistance is a central feature of the endocrine response to surgical tissue

trauma triggering metabolic changes known as the catabolic response to surgery. Insulin resistance is a state of decreased biological effect to any given concentration of insulin or a state of decreased

biologic response to physiologic concentrations of insulin. ⁽⁶⁾

Stress hyperglycemia is a catabolic state associated with adverse electrolyte and volume shifts. The mechanisms for this disorder probably vary with the patients' underlying glucose tolerance, type and severity of disease, and stage of illness. ⁽⁷⁾

Thus stress adversely affects multiple biological processes resulting in diminished insulin action and if the pancreas is unable to compensate by increasing insulin production, the end result is the appearance of hyperglycemia. Furthermore, in the presence of hyperglycemia, the pancreatic β -cells develop desensitization that results in further blunting of insulin secretion and increasing serum glucose levels. ⁽⁸⁾

Factors associated with perioperative hyperglycemia:

1. Known diabetes mellitus.
2. Catecholamine infusion, particularly epinephrine and norepinephrine.
3. Elderly.
4. Obesity.
5. Increase severity of illness.
6. Excess carbohydrate ingestion or infusion.
7. Acute or chronic pancreatitis.
8. Severe inflammation or infection.
9. Hypothermia.
10. Uremia.
11. Cirrhosis.
12. Hypoxemia. ⁽⁴⁾

Molecular mechanisms of perioperative insulin resistance

The effect of severe trauma, disease, infection, and surgery can result in remarkable metabolic stress on the human body. Survival of such insults depends in great part upon a functioning neuroendocrine system. The initial response to stress results in energy conservation toward vital organs, modulation of the immune system and a delay in anabolism. This acute response to stress is generally considered to be an appropriate one. When it occurs acutely, in some individuals, the pancreas may not be able to respond with appropriate hyperinsulinemia, and the result is hyperglycemia. ⁽⁹⁾

Although the biochemical manifestation of this transient state of insulin resistance is obvious, the underlying mechanisms remain poorly understood. Several alterations in the skeletal muscle, adipose tissue, neuroendocrine system and cytokines are proposed to explain the pathogenesis of perioperative insulin resistance. ⁽¹⁰⁾

Cellular effects of perioperative hyperglycemia:

Reports have begun to shed some light on alterations in normal cell functions at the molecular level. Acutely elevated glucose levels depress endothelin-induced calcium signaling in mesangial

cells, thereby depressing the contractile state of glomerular cells. Such information supports the hypothesis that acute hyperglycemia can affect cellular functions and may lead to clinically evident pathology. ⁽¹¹⁾

At the cellular level increased blood glucose levels results in mitochondrial injury by generating reaction oxygen species and endothelial dysfunction by inhibiting nitric oxide production. Hyperglycemia increases levels of pro-inflammatory cytokine such as TNF α , and IL-6 leading to immune system dysfunction, also increases plasminogen activator inhibitor-1 and fibrinogen causing platelet aggregation and hypercoagulable state. Hyperglycemia causes osmotic diuresis that leads to hypovolemia, decreased glomerular filtration rate, hypoperfusion, electrolyte loss, acid base disturbance and worsening hyperglycemia. These changes can eventually lead to increased risk of infection, impaired wound healing, prolonged hospital stay, multiple organ failure, and death. **(Fig. 4)** ⁽⁸⁾

Clinical Outcome of Perioperative Hyperglycemia

Researches into the mechanisms that cause the detrimental effects of perioperative hyperglycemia have mainly focused on modulation of inflammation, changes in vascular tone and alternation of coagulation. The effects of hyperglycemia on the heart, brain and endothelium have been the most researched. More importantly, there is increasing concern that stress hyperglycemia is different than hyperglycemia secondary to diabetes in that it confers an increased risk of mortality. ⁽¹²⁾

Higher mortality was noted in patients without diabetes requiring insulin compared to patients with known diabetes (10% vs 6%) in a retrospective single institution intensive care unit (ICU); despite lower average glucose values in the group without diabetes suggesting that hyperglycemia in this group may represent a different pathophysiology and natural history than in patients with known diabetes. It is estimated that for each 1 mmol/L (18 mg/dL) rise in admission fasting plasma glucose is associated with 33% increase in mortality. ^(8, 13)

Anesthesia and Blood Glucose Level

General anesthesia limits the perception of sensations during surgery but has little effect on the stress response to surgery, except for high-dose opioid anesthesia, which may inhibit intra- but not postoperative catabolic hormonal changes. It has been suggested that even deep general anesthesia cannot completely block the hypothalamic reaction to the noxious stimuli from an operation field. General anesthesia including medicines and laryngoscopy with tracheal intubation increases the response from the adrenergic system. Cortisol levels increase

significantly during operations under general anesthesia, mostly the peak increase occurs during intubation, skin incision and extubation.⁽¹⁷⁾

Neuraxial anesthesia is more effective than general anesthesia in attenuating the stress response. Activation of the sympathetic nervous system (SNS) and the hypothalamic–pituitary axis, induced by surgical stress under general anesthesia, provokes increases in circulating glucose, epinephrine, and cortisol concentrations, and these increases were prevented by spinal and epidural anesthesia.⁽¹⁸⁾

In a study on spinal and epidural anesthesia and analgesia compared with general anesthesia followed by patient controlled analgesia demonstrated a decrease in the incidence of insulin resistance soon after surgery only in patients who were insulin resistant before surgery. Spinal, epidural or other regional blockade modulate the secretion of catabolic hormones and insulin secretion.⁽¹⁹⁾

The ability of such anesthesia to modify the intraoperative stress response depends on the level of the blockade, the location of the surgery, and the drugs used.⁽¹⁹⁾

Combined general anesthesia and neuraxial anesthesia should reduce the stress response if the general anesthetic is sufficiently deep to attenuate the stimulation of the endotracheal tube.⁽²⁰⁾

Management of perioperative hyperglycemia

The treatment of stress hyperglycemia resolves itself into three separate approaches:

1. Maintenance of the hyperglycemia for those conditions in which there is a real or potential deficiency of CNS uptake that can be reversed by maintaining or even increasing the hyperglycemia.
 - These include hypovolemic and hypotensive states, in patients with cerebrovascular occlusive disease or with MI and low cardiac output or in hypoxic states.
2. Increasing glucose turnover by administering glucose and insulin or insulin alone for those conditions in which an increase of glucose use by insulin sensitive tissues is desired such as in burns, trauma or cold stress.
3. No treatment in those conditions in which there is no change of nutrient need. If hyperglycemia becomes severe, it can be treated with insulin alone, because the extra glucose being produced is not providing any needed function.⁽²¹⁾

This occurs in most pain related syndromes, particularly those in which significant amounts of trauma have not occurred and there is no need for increased glucose use or nutrient support for injured tissues. A similar situation occurs in hypothermia in which total body metabolism is reduced. In the absence of extra glucose administration, hyperglycemia is unusual. However, if glucose is

given to hypothermic humans, rather severe hyperglycemia can occur. Usually, all that is necessary is to stop the administration of exogenous glucose.^(21,22)

With recent outcomes studies like NICE-SUGAR and AACE/ADA association we prefer transition from the era of “tight” glycemic control to one of “less-tight” glycemic control, focusing intensely on the safety and efficacy of our glycemic control plan and avoidance, early detection and treatment of hypoglycemic events. Current recommendations for perioperative glucose management from national societies are varied, but, most suggest that tight glucose control may not be beneficial, while mild hyperglycemia appears to be well-tolerated.⁽²³⁾

Balancing the risks of hypoglycemia against the known benefits in morbidity and mortality is the goal, and, although intensive glycemic control continues to be standard of care, current consensus guidelines recommend less stringent glycemic goals, typically between 80-150 mg/dL.⁽²⁴⁾

The ultimate goal in the management of perioperative hyperglycemia is to improve the clinical outcomes. Optimization of the patient’s preoperative medications and the use of insulin infusions, as well as surgical and anesthetic technique, are important factors for achieving desirable perioperative blood glucose control. Minimizing blood glucose variability during surgery should be part of the glycemic control strategy. Advances in real-time glucose monitoring may benefit hospitalized diabetic and nondiabetic patients.⁽²⁵⁾

Comprehensive preoperative assessment and intensive intraoperative and postoperative management by a multidisciplinary team are recommended. A strong grasp of glucose insulin complexities and the effects of anesthesia and surgery are essential to optimizing outcomes.⁽²⁴⁾

Recommendations:

According to the evidence derived from this study, we recommend that early diagnosis and control of perioperative hyperglycemia lead to more control and less complications of hyperglycemia.

Conclusions Balancing the risks of hypoglycemia against the known benefits in morbidity and mortality is the goal, and, although intensive glycemic control continues to be standard of care, current consensus guidelines recommend less stringent glycemic goals, typically between 80-150 mg/dL.

Acknowledgements

The authors thank all supervisors and participants.

Correspondence author:**Name: Mohamed Hamdin Mandor M.B.B.Ch***

*Resident of Anesthesia Nasr city insurance hospital Cairo,

Address: Cairo.**Email:** aymanrady@yahoo.com**References**

1. Tsou S. Stress Hyperglycemia. *Tungs' Medical Journal* 2011; (5): 1-13
2. Grant RW, Clark NG, Desouza CV. American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care* January 2014; 37 (1):14-80.
3. Anthony S. Fauci, Braunwald E, Kasper D, Wongchaiya A. Harrison's Manual of Medicine 2014;17(2):100-3.
4. Frisch A, Candra P, Umpierrez G. Prevalence and Clinical Outcome of Hyperglycemia in the Perioperative Period in Noncardiac Surgery. *Diabetes Care* August 2010; 33 (8):1783-7.
5. Farrokhi F, Smiley D, Umpierrez G. Glycemic control in non-diabetic critically ill patients. *Best Practice & Research Clinical Endocrinology & Metabolism* 2011; (25): 813-24.
6. Schricker T. Perioperative insulin resistance and outcome. *EACTA* 2012; 78-83.
7. Pakhetra R, Garg MK, Suryanarayana KM. Management of Hyperglycemia in Critical Illness. *Medical Journal Armed Forces India* 2011; 67(1):53-57.
8. Farrokhi F, Smiley D, Umpierrez G. Glycemic control in non-diabetic critically ill patients. *Best Practice & Research Clinical Endocrinology & Metabolism* 2011; (25): 813-24.
9. Gibson SC, Hartman DA, Schenck JM. The Endocrine Response to Critical Illness: Update and Implications for Emergency Medicine. *Emerg Med Clin N Am* 2005; (23): 909-29.
10. Assmann AI, Spranger J. Pathophysiology of impaired insulin sensitivity in the perioperative period. *Anesthesiol Intensivmed Notfallmed Schmerzther.* 2011 Apr; 46(4):250-5.
11. Gautam A, Baluch A, Kaye A. Modern strategies for the anesthetic management of the patient with diabetes: *M.E.J.ANESTH* 2009; 20(2):187-97.
12. Knieriem M, Otto C, Macintire D. Hyperglycemia in Critically Ill Patients. *CE Article* June 2007; 2:360-72.
13. Sheehy AM, Gabbay RA. An Overview of Preoperative Glucose Evaluation, Management and Perioperative Impact. *Diabetes Sci Technol* November 2009; 3 (6), 1261-69.
14. Dufour S, Lebon V, Shulman G, Petersen K. Regulation of net hepatic glycogenolysis and gluconeogenesis by epinephrine in humans. *American journal of physiology. Endocrinology and metabolism.* 2009 Jul; 297(1): 231-5.
15. Ganong WL. Review of medical physiology. New York, McGraw-Hill 2001; 20: 322-43
16. Jeff D, Guarini K, Doong C. understanding the Mechanisms to Maintain glucose Homeostasis: a Review for Managed Care 2012; 18 (1):1-26.
17. Golubovska I, Vanags I. Anaesthesia and stress response to surgery. *Proc. Latv. Acad. Sci., Section B*, 2008; 62 (5), 141-47.
18. Donatelli F, Vavassori A, Bonfanti S, Parrella P, Lorini L, Fumagalli R, Carli F. Epidural anesthesia and analgesia decrease the postoperative incidence of insulin resistance in preoperative insulin-resistant subjects only. *Anesth Analg.* 2007; 104:1587-93.
19. Kadoi Y. Anesthetic considerations in diabetic patients. Part I: preoperative considerations of patients with diabetes mellitus. *J Anesth* 2010, 24:739-47.
20. Miller RD, Eriksson LI, Fleisher LA, Jeanine P. The Intraoperative Stress Response. *Nutrition and Metabolic Control, Miller's Anesthesia Preview* 2009; 2(39):2940-50.
21. Moses A. Stress Hyperglycemia. *The Association of Physicians of India* 2013; 38(5):178-81.
22. Havel P, Taborsky G. Stress-induced activation of the neuroendocrine system and its effects on carbohydrate metabolism. In: Porte D, Sherwin RS, Baron A (Eds). *Ellenberg & Rifkin's Diabetes Mellitus*, 6th edn. New York: McGraw-Hill. 2003; 127-49.
23. Duncan A. Hyperglycemia and perioperative glucose management. *Curr Pharm Des.* 2012; 18(38):6195-203.
24. Trivedi ML, Schwer WA. Perioperative Management of the Diabetic Patient. *Inpatient diabetes CME Updated Jun* 2013; 1-14.
25. Raju TA, Torjman MC, Goldberg ME. Perioperative Blood Glucose Monitoring in the General Surgical Population. *Journal of Diabetes Science and Technology* November 2009; 3 (6): 1282-7.

7/21/2014