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INSULIN THERAPY IN HOSPITALIZED PATIENTS

RĂZVAN VASILESCU [1], SILVI IFRIM [1] and CONSTANTIN IONESCU-TÎRGOVIŞTE [2]

[1]Clinical Hospital Colentina - Department of Diabetes, Nutrition and Metabolic Diseases
[2]National Institute of Diabetes, Nutrition and Metabolic Diseases "N.C.Paulescu"
Correspondence Author: Vasilescu Răzvan, razvanv@mailbox.ro

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Hyperglycemia occurs frequently in hospitalized patients and many studies have shown that hyperglycemia is associated with poor outcomes. Until recently was considered that hyperglycemia does not significantly influence the patients outcome. This changed with the publication of Van den Berghe study, which demonstrated significant reduction in mortality with intensive glycemic management. Recent studies have shown that targeting near euglycemia is associated with higher rates of severe hypoglycemia with no reduction in mortality. The consensus statement from American Association of Clinical Endocrinologists and American Diabetes Association recommends a target glucose range of 140–180 mg/dl in most hospitalised patients. Intravenous insulin infusions are recommended for critically ill patients and subcutaneous insulin algoritms with basal and rapid- or short-acting insulin administered before meals are recommended for non-critically ill patients. The American Heart Association Diabetes Committee recommendation is that in patients with acute coronary syndrome admitted to an ICU intensive glucose control, using insulin administered as an intravenous infusion, should be considered if plasma glucose is > 180 mg/dl. Recommended range for plasma glucose is 90–140 mg/dl, as long as hypoglycemia is avoided. In patients hospitalized in the non-ICU setting plasma glucose levels should be < 180 mg/dl with subcutaneous insulin regimens. The European Stroke Organisation guidelines for management of ischemic stroke published in 2008 recommend treatment of blood glucose levels > 180 mg/dl with insulin.

Key words: insulin therapy, hospitalized patients, hyperglycemia.

INTRODUCTION

Hyperglycemia is common in hospitalized patients and there is a direct relationship between hyperglycemia and acutely ill patients[1–3]. Hyperglycemia may occur in patients with known diabetes, undiagnosed diabetes and in patients with previously normal glucose tolerance[4,5]. Extensive evidence indicates that hyperglycemia in hospitalized patients is associated with poor outcomes[6–8]. Several studies reported a direct relationship between hyperglycemia and increased mortality and morbidity after cardiac surgery[6], in patients in medical care unit (ICUs)[9], patients with stroke[7,8] and patients with acute myocardial infarction[10].

Stress hyperglycemia is defined as a transient hyperglycemia during acute illnesses[11]. Excessive gluconeogenesis (especially through increase in glucagon secretion) and reduced insulin-mediated glucose uptake (especially by skeletal muscle) a result of decreased insulin sensitivity induced by cytokines (such as interleukin-1 – IL-1 and tumour necrosis factor-α – TNF-α) and counter-regulatory hormones (cortisol, catecholamines, growth hormone), cause stress hyperglycemia[11]. Contributing factors to hospital hyperglycemia include enteral and total parenteral nutrition, administration of vasopressors and exogenous glucocorticoids, pancreatic reserve and insulin resistance prior to admission[11]. Finally, one must take into account that blood glucose values could be artificially increased in patients hospitalized in intensive care units if the samples were obtained during an infusion of glucose (even glucose 5%). In this case the blood glucose values could be very high.

There are differences regarding the correlation between hyperglycemia and outcome of patients, by the presence of diabetes at admission[2,12]. Whitcomb *et al.*[12] showed that hyperglycemia was an independent risk factor only in patients without diabetic history in the cardiac, cardiothoracic and neurosurgical ICUs. Umpierrez *et. al.*[2] showed in non-ICU patients that subjects with newly diagnosed hyperglycemia had significantly higher mortality rate than subjects with a prior history of diabetes and subjects with normoglycemia (18.3-fold increase in mortality rate in patients with newly diagnosed hyperglycemia compared with a 2.7-fold increase in patients with a prior history of diabetes *versus* subjects with normoglycemia).

Management of inpatient hyperglycemia has changed during the last decade[5]. Until recently was considered that hyperglycemia does not significantly influence the patients outcome. This changed with the publication of Van den Berghe study[13], which demonstrated significant reduction in mortality with intensive glycemic management. Recent studies have shown that targeting near euglycemia is associated with higher rates of severe hypoglycemia with no reduction in mortality[14,16].

In this paper we review the major studies that investigate the inpatient management of hyperglycemia and summarize the practice guidelines.

MANAGEMENT OF HYPERGLYCEMIA IN PATIENTS IN INTENSIVE CARE UNITS

Studies that evaluated the effects of tighter glucose control have had conflicting results[13–16]. In 2001 Van den Burghe *et al.*[13] reported the results of a prospective, randomized study that enrolled 1548 patients (13 percent of the patients had a history of diabetes and 5 percent were receiving treatment with insulin), admitted to a surgical intensive care unit, who were assigned in two groups according to type of treatment (intensive or conventional). In the intensive treatment group an insulin infusion was started if the blood glucose level exceeded 110 mg/dl with a target of 80 to 110 mg/dl (mean value obtained 103±19 mg/dl), while in the conventional treatment group infusion of insulin was administered only if the blood glucose exceeded 215 mg/dl with a target of 180 to 200 mg/dl (mean value obtained 153±33 mg/dl). The study showed that intensive treatment is associated with a 42% relative reduction in mortality, especially in patients who required intensive care for more than five days. Intensive insulin therapy also reduced episodes of septicemia by 46%, acute renal failure requiring dialysis or hemofiltration by 41%, the median number of red-cell transfusions by 50% and critical-ilness polyneuropathy by 44%. Five years later, in 2006, Van den Berghe *et al.*[14] published the results of a study that included 1200 patients admitted to a medical ICU. In this study, the investigators reported that intensive insulin therapy, compared to conventional therapy did not significantly reduce in-hospital mortality (37.3% *versus* 40.0, $p = 0.33$). In contrast, in patients who stayed in the ICU for three or more days, in-hospital mortality was significantly reduced in the intensive treated group (43.0% *versus* 52.5%, $p = 0.009$).

A metaanalysis[15] published in 2008 that included 29 randomized controlled trials totaling 8423 subjects showed that in critically ill adult patients tight glucose control was not associated with significantly reduced hospital mortality (21.6% *versus* 23.3%), even when where stratified by glucose goal (very tight ≤110 mg/dl, 23% *versus* 25.2%, moderately tight <150 mg/dl, 17.3% *versus* 18%) or intensive care unit setting (surgical, 8.8% *versus* 10.8%, medical, 26.9% *versus* 29.7% and medical-surgical, 26.1% *versus* 27%) but was associated with significantly increased risk of hypoglycemia (13.7% *versus* 2.5%).

In 2009 were reported the results of the study NICE-SUGAR (Normoglycemia in Intensive Care Evaluation – Survival Using Glucose Algorithm Regulation)[16] that enrolled 6104 patients admitted to ICU, who were assigned in two groups according to type of glucose control: intensive, with a target blood glucose range of 81 to 108 mg/dl (mean value obtained 115±18 mg/dl) and conventional, with a target blood glucose <180 mg/dl (mean value obtained 144±23 mg/dl). In this study the investigators found that intensive glucose control, as compared with coventional glucose control, increased the risk of death at 90 days (27.5% *versus* 24.9%) and the number of patients with severe hypoglycemia (6.8% *versus* 0.5%).

Guidelines for inpatient glycemic control

In 2009 were published the American Association of Clinical Endocrinologists and American Diabetes Association recommendations on inpatient glycemic control[4] for both critically ill patients and patients hospitalized in medical and surgical non-ICU

settings. In January 2012 was published the Endocrine Society, American Diabetes Association, American Heart Association, American Association of Diabetes Educators, European Society of Endocrinology and the Society of Hospital Medicine practice guideline on the management of hyperglycemia in hospitalized patients in the non-critical care setting[17]. Insulin is the preferred agent for glycemic control in hospitalized patients, focusing on the safety and efficacy of the glycemic control plan[18]. Critically ill patients should receive intravenous insulin infusion at glucose value >180 mg/dl, with a target 140–180 mg/dl. Non-critically ill patients should receive subcutaneous insulin consist of basal or intermediate-acting insulin given once or twice a day in combination with rapid- or short-acting insulin administered before meals in patients who are eating, with premeal glucose target <140 mg/dl and random glucose target <180 mg/dl. For patients with limited life expectancy or at high risk for hypoglycemia, a higher glucose target < 200 mg/dl is recommended. Home oral hypoglycemic agents should be replaced by insulin therapy for most patients.

MANAGEMENT OF HYPERGLYCEMIA IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION (AMI)

Abnormal glucose regulation is common in patients with acute coronary syndrome (ACS). The prevalence of diabetes mellitus among patients hospitalized for AMI in the United States increased substantially from 18% in 1997 to 30% in 2006[19]. Euro Heart Study[20] showed in patients with CAD without known diabetes, admitted for an acute illness (ACS, aggravated symptoms of heart failure, arrhythmias due to CAD) that 36% had impaired glucose regulation and 22% newly diagnosed diabetes and in the stable patients with scheduled admissions that 37% had impaired glucose regulation and 14% newly diagnosed diabetes. De la Hera *et al.*[21] showed in patients who undergo percutaneous coronary intervention that 28.8% had known diabetes, 16.2% had newly diagnosed diabetes and 25.5% had impaired glucose regulation.

A meta-analysis published in 2010, that included data for 698.782 subjects from 102 prospective studies showed that diabetes confers a two-fold excess risk for coronary heart disease[22]. Patients with diabetes compared with non-diabetic subjects have a substantially increased risk of death after AMI[23–26]. Kjaergaard *et al.*[26] showed that diabetic patients with AMI had 28% in-hopital mortality compared to 13% in nondiabetic patients with AMI. In diabetic patients hyperglycemia both at admission or during hospitalization is associated with a higher mortality rate. Otter *et al.*[25] reported that diabetic patients with AMI had higher mortality rate both within 24 hours after admission (13.5% *versus* 5.4%) and during hospitalisation (29.4% *versus* 16.2%).

Hyperglycemia at admission is associated with increased mortality rate in patients with AMI both in diabetic and non-diabetic subjects[27–29]. Wahab *et al.*[27] showed in nondiabetic patients with AMI that glucose levels >198 mg/dl were associated with a 2.44-fold increased risk of in-hospital mortality. Capes *et al.*[28] showed in a meta-analysis that patients without diabetes who had glucose values more than or equal to range 110–144 mg/dl had a 3.9-fold higher risk of death than patients without diabetes who had lower glucose concentrations. In patients without diabetes glucose concentrations higher than values in the range of 144–180 mg/dl on admission were associated with increased risk of congestive heart failure or cardiogenic shock. Patients with diabetes who had glucose concentrations more than or equal to range 180–198 mg/dl had a moderately increased risk (1.7 fold) of death.

The results of the studies that evaluated the treatment of hyperglycemia in pacients with AMI are contradictory[30]. In 1995 were published the results of DIGAMI-1 study (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction)[31] that showed a 29% relative reduction (18.6% *versus* 26.1%) in 1-year mortality in AMI patients with glucose values > 198 mg/dl treated with insulin-glucose infusion during the first 12 h and continued subcutaneously for 3 months. The study included 620 patients, divided in two groups, according to hyperglycemia treatment (infusion vs. conventional). The two groups were well matched for baseline characteristics (age: 69 years, infusion *versus* 68 years, control; diabetes duration at admission: 10 years, infusion *versus* 10 years, control; HbA1c: 8.2% infusion *versus* 8% control; basal glycemia: 277mg/dl, infusion *versus* 283mg/dl, control). The mean time from onset of symptoms to randomization was 13±7 h. The mortality reduction was particularly evident in patients who had a low cardiovascular risk profile and no previous insulin treatment (52% relative reduction at 3-month – 6.5% *versus* 13.5% and 1-year –

8.6% *versus* 18%). The study showed that both cardiovascular mortality and the number of reinfarctions were decreased in insulin treated patients but this differences did not reach the level of statistical significance[32]. During an average follow-up of 3.4 years in the insulin treated group there was a relative mortality reduction of 28%[33]. The mortality reduction was particularly evident in patients who had a low predicted cardiovascular risk and no previous insulin treatment (51% relative reduction – 19% *versus* 70%). Severity of the glycometabolic state at admission, evaluated by blood glucose and HbA1c values, is an independent predictor of mortality during long-term follow-up.

The results of the DIGAMI 1 study were not confirmed in the DIGAMI 2 study, published in 2005[34]. DIGAMI 2 included 1253 patients (mean age 68 years, 67% males) with diabetes and suspected acute myocardial infarction classified in three groups according to the treatment of hyperglycemia: a) a 24 h insulin-glucose infusion followed by a subcutaneous insulin-based long term glucose control (group 1); b) a 24 h insulin-glucose infusion followed by standard glucose control (group 2); c) routine metabolic management according to local practice (group 3). The groups were well matched for baseline characteristics. The mean diabetes duration was 8 years, the mean value of HbA1c was 7.3% and the mean value blood glucose was 229 mg/dl. The treatment goal for patients in group 1 was a fasting blood glucose level of 90–126 mg/dl and a non-fasting level <180 mg/dl. The mean study duration was 2.1 years. The study reported that there were no differences between groups as regards mortality outcome (23.4% *versus* 21.2% *versus* 17.9%).

Several factors may influence the results of DIGAMI 2 study[34,35]: 1) the acute decrease in glycemia in the intensive treated group in 24 h was modest (59mg/dl), without reaching the target and not different between groups; 2) no differences in HbA1c (6.8%) and basal glycemia (149mg/dl) were achieved; 3) in patients treated intensively the initial decrease in blood glucose was more substantial in DIGAMI 1 than in DIGAMI 2 (104 mg/dl *versus* 59 mg/dl); 4) at 1 year, intensive treatment reduced HbA1c more substantial in DIGAMI 1 than in DIGAMI 2 (0.9% *versus* 0.5%), in addition the decrease was even more substantial (1.3%) in the subgroup with low cardiovascular risk in DIGAMI 1; 5) 1 year mortality in DIGAMI 2 was 65% lower than in DIGAMI 1, due to progress on the management of IMA. Based on the association between hyperglycemia and decrease plasma fibrinolytic activity Taylor[36] stressed the importance of reducing hyperglycemia effectively in the first few hours from the admission. With this aim, the author propsed a two-step strategy: 1) bring down blood glucose to target levels by use of insulin with frequent checks of blood glucose and 2) maintain steady blood glucose levels by glucose-insulin infusion.

Effect of glucose-insulin-potassium infusion in patients with AMI

The concept of glucose-insulin-potassium (GIK) infusion in patients with AMI was proposed in 1962 by Sodi-Pallares *et al.*[37]. Then, a metaanalysis published in 1997[38] showed a reduction in mortality from 21% to 16.1% in patients treated with GIK. Recent studies demonstrated that with the implementation of new therapies for AMI, GIK infusion had no impact on the outcome of the patients[39–41].

Recommendations for hyperglycemia management in patients with acute coronary syndrome

In 2008 was published a scientific statement from the American Heart Association Diabetes Committee regarding the management of hypeglycemia in patients with ACS[42]. The level of evidence A recommendation is that glucose level should be measured in all patients with suspected or confirmed ACS. The level of evidence B recommendation is that in patients with ACS admitted to an ICU glucose levels should be monitored closely and intensive glucose control may be considered if plasma glucose is >180mg/dl, regardless of prior diabetes history. It is recommended to use insulin administered as an intravenous infusion in patients hospitalized in the ICU (level of evidence B). Recommended range for plasma glucose is 90–140 mg/dl, as long as hypoglycemia is avoided (level of evidence C). The level of evidence C recommendation is that in patients hospitalized in the non-ICU setting plasma glucose levels should be < 180 mg/dl with subcutaneous insulin regimens. Pacients with hyperglycemia but without prior history of diabetes should have further evaluation (preferably before hospital discharge) to determine the severity of their metabolic dereangements (HbA1c assessment and in some cases, a postdischarge oral glucose tolerance test) (level of evidence B). Before

discharge, plans for optimal outpatient glucose control should be determined in those patients with established diabetes, newly diagnosed diabetes or evidence of insulin resistance (level of evidence C).

MANAGEMENT OF HYPEGLYCEMIA IN PATIENTS WITH ACUTE ISCHEMIC STROKE

The incidence of hyperglycemia in patients with acute ischemic stroke is estimated at 50% and the prevalence of previously diagnosed diabetes mellitus is estimated between 8% and 20%[43-46]. Gray *et. al.*[44] showed for patients presenting with post-stroke hyperglycemia, 37% had impaired glucose tolerance and 21% had diabetes mellitus at 12 weeks.

The association between hyperglycemia and adverse outcome in patients with acute ischemic stroke have been established by numerous studies[7,45-47]. Parsons *et al.*[47] showed that acute hyperglycemia increases brain lactate production and facilitates conversion of hypoperfused at-risk tissue into infarction, which may adversely affect stroke outcome. Capes *et al.*[7] showed in a meta-analysis that in patients with no history of diabetes who have an ischemic stroke, hyperglycemia is associated with both a 3-fold higher risk of mortality and an increased risk of poor functional recovery compared with lower glucose levels. Some studies showed a relationship between hyperglycemia and hemorrhagic transformation after ischemic stroke[10,48,49]. Ahmed *et al.*[10] showed in 16049 patients with acute ischemic stroke treated with thrombolysis that in nondiabetic subjects hyperglycemia was independently associated with higher mortality, lower independence and an increase risk of symptomatic intracerebral hemorrhage. In diabetic subjects hyperglycemia was statistically significant associated only with lower independence. In diabetic subjects blood glucose values associated with increased mortality and lower independence are greater compared to nondiabetic subjects. Ntaios *et al.*[50] showed in 1446 patients with acute ischemic stroke a J-shaped curve association with a nadir of 90 mg/dl between serum glucose and 24 hour and 12 month outcome. Initial serum glucose values between 67 mg/dl and 131 mg/dl are associated with favorable outcome.

Severeal studies evaluated the association between temporal profile of poststroke hyperglycemia and outcome in patients with acute ischemic stroke[51–53]. Allport *et al.*[51] using a continuous glucose monitoring system evidentiated in nondiabetic as well in diabetic patients with acute ischemic stroke, a late hyperglycemic phase, for at least 88 hour poststroke. In diabetic patients at 8 hour from stroke onset 100% were hyperglycemic, at 14–16 hour 27% were hyperglycemic and at 48–88 hour 78% were hyperglycemic. In nondiabetic patients at 8 hour from stroke onset 50% were hyperglycemic, at 14–16 hour 11% were hyperglycemic and at 48-88 hour 34% were hyperglycemic. Christensen *et al.*[52] showed in patients with acute stroke with no history of diabetes mellitus that blood glucose increases within the first 12 hour after the onset of stroke and the increase is related to the severity of the stroke. Yong *et al.*[53] analysed in 748 patients with acute ischemic stroke included in the second European Cooperative Acute Stroke Study (ECASS-II) the dynamics of serum glucose levels within the first 24 hours and its impact on stroke outcome. In nondiabetic patients persistent hyperglycemia (hyperglycemia at baseline and at 24 hours) was inversely associated with neurological improvement and it was associated with an increased risk of mortality and intracerebral hemorrhage whereas hyperglycemia at baseline only was not associated with any parameter of worse outcome. In diabetic patients the dynamic patterns of hyperglycemia was not associated with stroke outcome. Recent studies have demonstrated that not only admission glucose values but also the development of hyperglycemia on serial glucose evaluations are associated with poor outcome[54]. Fuentes *et al.*[55] showed in 476 patients with acute ischemic stroke that hyperglycemia ≥ 155 mg/dl at any time within the first 48 hours from stroke onset is associated with poor outcome independently of stroke severity, infarct volume, diabetes and age.

Intensive insulin therapy compared to conventional therapy in patients with acute ischemic stroke

Several studies have demonstrated that insulin infusion for patients with acute ischemic stroke is safe[56]. The studies that evaluated the outcome of the patients with acute stroke by the type of glycemic treatment (intensive vs. conventional) found no difference. The GIST-UK study[57] showed in patients with acute stroke that there was no significant reduction in mortality at 90 days in the GIK infusion group for 24 hours, with a target capillary glucose of 72–126 mg/dl, compared to

control group, wih no glucose intervention. Bruno *et al.*[58] evaluated the feasibility and tolerability of aggressive hyperglycemia treatment with intravenous insulin in patients with acute ischemic stroke. The study included 46 patients, with a baseline glucose value ≥150 mg/dl, 91.3% had diabetes, who were randomized in two groups: 1) aggressive treatment group, with hyperglycemia correction with continuous intravenous insulin and target glucose levels <130 mg/dl (mean value obtained 133 mg/dl) and 2) usual care group, with hyperglycemia correction with subcutaneous insulin and target glucose levels <200 mg/dl (mean value obtained 190 mg/dl). The results of the study showed that in diabetic patients with acute ischemic stroke clinical outcomes at 3 months from the acute event in the intensive treatment group were not significantly better than in the usual care group. Hypoglycemia occurred only in the aggressive treatment group (a total of 12 episodes).

Frontera[59] found in 81 critically ill neurologic patients that there was no survival or outcome benefit to intensive insulin treatment over conventional insulin therapy. Patients randomized to intensive therpy were treated with a continuous insulin infusion for a goal glycemic value of 80–110 mg/dl (mean value obtained 112 mg/dl), evaluated every 1 hour initially and every 2 hours as levels stabilized. In patients randomized to conventional treatment, subcutaneous insulin was initiated whenever glycemia was >150 mg/dl (mean value obtained 143 mg/d), evaluated every 6 hours. Hypoglycemic episodes were more frequent in the intensive treated patients (21 patients treated intensive, representing 47% vs. 4 patients treated conventional, representing 11%). Van den Berghe *et al.*[13] found no difference in hospital mortality between the intensive insulin and conventional group. Bruno *et al.*[60] recommend in patients with acute ischemic stroke treated with thrombolytic drugs and admission blood glucose >300 mg/dl giving an intravenous bolus of regular insulin of 8U, followed by a temporary continuous intravenous insulin infusion to maintain the glucose values closer to normal (approximately 140 mg/dl).

Recommendations for hyperglycemia management in patients with acute ischemic stroke

New evidence has resulted in changes in the recommendations regarding management of hyperglycemia in patients with acute stroke. In 2003 a scientific statement from the Stroke Council of the American Stroke Association recommended to lower markedly elevated glucose levels to < 300 mg/dl[61] and in 2007 a guideline from the American Heart Association and American Stroke Association Stroke Council recommended intiation of insulin therapy if blood glucose vaues > 145 mg to 185 mg/dl. The European Stroke Organisation guidelines for management of ischemic stroke published in 2008 recommend treatment of blood glucose levels > 180 mg/dl with insulin[63].

CONCLUSIONS

Expanding use of teste strips for blood glucose monitoring in the hospital setting has increased the interest in improving glucose control in hospitalized patients. Many studies have evaluated this subject. The results of these studies showed an increase in concordance with the clinician judjment who choosed the “middle way”, that a significant hyperglycemia (>200 mg/dl) does not require an **aggressive** correction (inapropriate medical term, expressing an excessive behaviour) which in most of the cases proves useless or even harmful. A slower decline of blood glucose levels keep the benefits of reducing hyperglycemia at a reasonable level (140 mg/dl), avoiding the risks that a sudden drop in blood glucose levels may entail. In patients with acute events (acute ischemic stroke, acute coronary syndrome) moderately increased blood glucose levels (140–160 mg/dl) is preferred to blood glucose levels <80 mg/dl.

Elevated blood glucose is frequent in patients hospitalised in the ICU and a careful interpretation leads to a correct therapeutic approach during acute period. In hyperglycemic patients without known diabetes before admission for an acute event the glycemic status should be reevaluated at 3 months after discharge in a diabetic center, where diabetic patients will be registered.

One last point: increased prevalence of newly diagnosed diabetes in patients hospitalized for acute stroke or acute coronary syndrome suggest that these patients have not been sufficiently evaluated by the family physicians or patients with mild hyperglycemia (110–130 mg/dl) were not

referred to confirm diabetes diagnosis to a diabetic center, which cover all the country.

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