The association between blood glucose levels and hospital outcomes in patients admitted with acute exacerbations of chronic obstructive pulmonary disease

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ABSTRACT

Patients with acute exacerbations of chronic obstructive pulmonary disease usually require an escalation in medical management and often require hospitalization. The outcomes from these episodes depend on the severity of the underlying chronic lung disease, the degree of acute respiratory failure superimposed on the chronic lung disease, comorbidity, and possibly hospital related complications. Hyperglycemia represents an independent risk factor for hospital associated complications and/or mortality in other medical diagnoses, such as stroke and acute myocardial infarction. Recent studies in patients with acute exacerbations of COPD demonstrate that hyperglycemia is associated with an increased length of hospital stay, failure of noninvasive ventilation, and/or mortality. Acute stress and medications used with an acute flare, such as glucocorticoids and beta agonists, increase blood glucose levels. The explanation for poor outcomes likely involves an increase in colonization with pathogenic bacteria, acute changes in host defenses, and possibly metabolic disorders related to hyperglycemia and glycosuria. Patients with acute stress and glucocorticoid related hyperglycemia often have higher blood glucose levels in the afternoon and early evening. Consequently, this problem may be overlooked if clinicians depend on routine a.m. laboratory tests. Therefore, patients with acute flares in COPD should have bedside point of care glucose measurements during the early course of their hospitalizations. Patients with high glucose levels require nutritional management and/or insulin treatment. We need more prospective studies to determine the degree of hyperglycemia in these patients, the acute consequences, and the best management strategies.

Keywords: COPD exacerbation, hyperglycemia, length of stay, mortality and morbidity.

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) have acute exacerbations approximately 1.3 times per year. These exacerbations range in severity from transient decreases in functional status to fatal events. In the United States, exacerbations have contributed to a 102 percent increase in COPD-related mortality from 1970 to 2002 (21.4 to 43.3 deaths per 100,000 persons)[1]. Effective management of an acute exacerbation of COPD (AECOPD) requires symptom relief and reducing the risk for subsequent exacerbations. Identification of patients at risk for more complicated hospital courses should facilitate in-patient management, and risk factors for adverse outcomes include lower arterial pHs, older age, male gender, underlying comorbidities, disease severity, and in-hospital complications[2]. Hyperglycemia is associated with poor outcomes in patients with pneumonia[3], myocardial infarction[4], and stroke[5], but the effect of hyperglycemia on outcomes during AECOPD has not been definitely established. Recent

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Global Initiative of Chronic Obstructive Lung Disease (GOLD) and American Thoracic Society guidelines do not comment on the control of blood glucose during COPD flares.

The effect of hyperglycemia on outcomes of acute COPD exacerbation

Hyperglycemia is very common in any acute illness, and its pathophysiology includes acute increases in peripheral insulin resistance and hepatic glucose production caused by increases in glucocorticoids, catecholamines, and pro-inflammatory cytokines[6]. Below we summarize studies that have evaluated the effect of hyperglycemia in patients admitted with AECOPD (Table).

Baker, et al. concluded that hyperglycemia (blood glucose >126 mg/dl) is associated with an increased risk of death and prolonged hospital stays (more than nine days) independent of age, sex, and a previous diagnosis of diabetes[7]. This study also showed that in the subgroup of patients who had COPD confirmed by spirometric testing, the blood glucose quartile independently predicted adverse clinical outcomes, but the underlying COPD severity did not. This was a retrospective case control study conducted by retrieving data from electronic medical records for 284 patients admitted with AECOPD to St. George's Hospital (UK) between 2001 and 2002. In this study, only the highest blood glucose recorded for the patients during their hospital stay was used for analysis, and patients were grouped according to their blood glucose quartile (group 1, <108 mg/dl, n = 69; group 2, 108–125 mg/dl, n = 69; group 3, 126–160 mg/dl, n = 75; and group 4, >160 mg/dl, n = 71).The relative risk (RR) of death or a longer inpatient stay was significantly increased in group 3 (RR 1.46, 95% CI 1.05 to 2.02, p = 0.02) and group 4 (RR 1.97, 95% CI 1.33 to 2.92, p<0.0001) compared to group 1. For each 18 mg/dl increase in blood glucose the absolute risk of an adverse outcome increased by 15% (95% CI 4%to 27%, p = 0.006). Also hyperglycemia was associated with colonization of sputum with multiple pathogens and with *Staphylococcus aureus* in this study.

The relationship between hyperglycemia and non-invasive ventilation (NIV) outcomes in COPD patients was investigated in a prospective study by Chakrabarti, et al.[8]. These authors concluded that hyperglycemia on admission is associated with NIV failures. Eighty-eight COPD patients presented with acute type II respiratory failure and had NIV initiated within 24 hours of admission. Random blood glucose levels were measured before NIV use. Hyperglycemia was present at baseline in 50% of patients; 16 (18%) had a pre-existing diagnosis of diabetes mellitus. NIV failure occurred in 34% of patients (15/44). It was significantly more common in patients with hyperglycemia (34%) than in patients without hyperglycemia (2%). Blood glucose levels were higher in patients with NIV failure (162.7 ±58 mg/dl vs. 127±39.2 mg/dl; p=0.003). It is not known whether hyperglycemia is a direct cause of poor outcomes in AECOPD or whether it is a marker for other adverse factors, such as coexisting comorbidities, treatment strategies, or the severity of illness. This study provided some insight into the possible underlying mechanisms since the NIV failure in AECOPD was independent from oral corticosteroid use immediately before admission, underlying diabetes mellitus, pH and APACHE II (Acute Physiology and Chronic Health Evaluation II) scores.

Moretti and colleagues studied 186 patients admitted to a respiratory intensive care unit with respiratory failure characterized by a mean pH of 7.23± 0.07 and a mean PaCO2 of 85.3 ±15.8 mm Hg[9]. The study used logistical regression analysis to analyze factors associated with noninvasive respiratory failure after an initial success (late failures). The presence of metabolic complications (found in >20% of the late failures) predicted late failures (more than 48 hrs) of NIV after an initial success. The most frequent metabolic complication was hyperglycemia (defined as blood glucose >200 mg/dl) which was present in all the patients with metabolic disorders. However, all hyperglycemic patients who developed late failure to NIV also developed pulmonary infection during the course of their hospital stays, and this likely contributed to NIV failure or death.

Burt, et al. reported that length of hospital stay

is increased by 10% (21hours) for each 18 mg/dl increase in mean glucose (P=0.01)[10]. In this study the blood glucose levels of 47 patients were monitored continuously using a device to measure interstitial glucose levels to determine the pattern of hyperglycemia in patients receiving prednisolone for AECOPD. Higher mean daily glucose levels were positively associated with longer hospital stays; this relationship with length of stay was not significant for other markers of disease severity. Parappil et al. retrospectively analyzed 172 patients admitted with AECOPD, including 39 patients with comorbid diabetes mellitus [11]. In this study the presence of DM was associated with increased length of stay (mean 7.8 days) and mortality (8%) in comparison with patients without DM (6.5 days and 4% mortality), but these differences were not statistically significant.

Kasirye, et al. studied 209 hospitalized patients with AECOPD to evaluate factors associated with in-hospital complications, length of hospitalization, 30-day hospital readmission, and 90-day all-cause mortality. The study analysis failed to reveal any associations between higher blood glucose levels and adverse outcomes but did find that low glucose levels (less than 90 mg/dl) were associated with increased hospital complications and increased length of stay in these patients[12]. This study had three important differences when compared to the Baker study. 1) It used WHO/GOLD criteria and previous spirometric measurements to define population with AECOPD, while the Baker study used only ICD-10 codes. 2) This study used radiological information to rule out other comorbidities, like pneumonia, which might confer a confounding effect on the data. 3) This study used daily mean blood glucoses to identify hyperglycemia, since blood glucose levels among AECOPD patients on systemic corticosteroids tend to peak in the afternoon and evening hours. Therefore, blood glucose measurements taken throughout the day more accurately reflect a patient's glycemic status. Other studies have utilized either single admission blood glucose or a single peak blood glucose obtained fasting or non-fasting during hospitalization.

Hypoglycemia is not a usual finding in AECOPD, because hyperglycemia often develops secondary to stress hormones release, cytokines[13], and treatment with systemic corticosteroids [14]. The presence of hypoglycemia may be a marker for severity of illness if its presence is not related to a treatment side effect. It could reflect defects in glucose counter-regulation. Therefore, the patient's inability to develop a hyperglycemic response might portend adverse clinical outcomes [15,16].

Studies demonstrating that hyperglycemia is associated with poor outcomes in AECOPD usually do not identify the possible pathophysiology. In one cross sectional observation study, the glucose levels of intubated patients were measured in bronchial secretions and blood, and the sputum was cultured for pathogenic bacteria[17]. This study demonstrated that glucose was detected in airway secretions in patients with hyperglycemia and the risk of colonization with MRSA was markedly increased in the presence of glucose (relative risk 2.1; 95% CI 1.2 to 3.8). In addition, the presence of MRSA was associated with infiltrates on the chest radiograph, increased levels of C reactive protein, and prolonged ICU stays (approximately seven days) [17].The Baker study also showed that hyperglycemia was associated with a significant increase in the presence of multiple pathogens and MRSA in the sputum[18]. Hyperglycemia may increase the rate of colonization, and these changes in flora in association with abnormal host defenses increase the risk of infection and adverse outcomes.

AECOPD MANAGEMENT AND GLUCOSE METABOLISM

Hyperglycemia (defined as blood glucose level more than 200 mg/dl) in acutely ill patients with no prior diagnosis of diabetes, including those admitted for AECOPD, has been linked to several factors, including medications and stress responses to acute illness. It has been reported that more than 38% of patients admitted to the hospital have hyperglycemia (defined by in-hospital fasting glucose level of ≥126 mg/dl or a random blood glucose level of 200 mg/dl)[19]. COPD itself may be considered as a novel risk factor for new onset type 2 diabetes mellitus through multiple pathophysiological alterations, such as inflamma-

tion, oxidative stress, insulin resistance, weight gain, and alterations in metabolism of adipokines[20,21,22]. Moreover, infection (a potential cause of AECOPD) can lead to hyperglycemia by the development of peripheral insulin resistance and alterations in hepatic glucose metabolism, leading to the overproduction of glucose and failure of the liver to appropriately adapt when nutritional support is administered[23]. We will discuss briefly the factors that can affect glucose metabolism in AECOPD patients.

Neuroendocrine and inflammatory stress responses

In acute illness, glucose production is increased, peripheral glucose utilization is decreased, and this leads to increased plasma glucose levels. This response appears to be mediated by a combination of neurohumoral changes, lipid mediators, and cytokine production. Increased serum concentrations of glucagon, adrenaline, and cortisol occur in response to a variety of pathophysiological stresses. As a part of the acute stress response, reversible insulin resistance develops, and peripheral glucose uptake decreases [24]. Stress in acutely ill patients can also lead to increased catecholamine secretion, which can contribute to hyperglycemia [25].

Hypoxia

Oltmanns, et al. studied 14 healthy male volunteers. These men were subjected to 30 minutes of hypoxia (O2 saturation =75%) and normoxia (O2 saturation= 96%) under conditions of a euglycemic clamp [26]. This study concluded that acute hypoxia causes glucose intolerance. Hypoxia also increased plasma epinephrine levels, heart rates, and anxiety. Several animal studies have shown the development of insulin resistance after periods of intermittent hypoxia [27,28]. Louis and Punjabi studied the effect of intermittent induced hypoxia on 13 healthy volunteers using an intravenous glucose tolerance test to assess insulin dependent and independent glucose disposal. The study showed that intermittent hypoxia caused insulin resistance and defective insulin independent glucose disposal [29]. Pallayova, et al. concluded that intermittent hypoxia is associated with damage to pancreatic beta cells[30]. Animal studies have also demonstrated that both acute and chronic sustained hypoxia can cause insulin insensitivity and hyperglycemia[31].

Acidosis

AECOPD can be complicated by hypercapneic respiratory failure and respiratory acidosis. Studies have shown that respiratory acidosis causes glucose intolerance by inducing hepatic and peripheral insulin resistance [32]. In addition, animal studies suggest that metabolic acidosis can cause impaired insulin secretion [33].

Medications

a.*Glucocorticoids*: Hyperglycemia is a well-recognized complication of corticosteroid therapy. At the University of Pittsburgh, a retrospective study concluded that hyperglycemia occurs in the majority of hospitalized patients receiving high doses of corticosteroids (≥40 mg per day) [34]. Since poor outcomes are associated with hyperglycemia, these authors suggested that a protocol should be followed to measure glucose levels in all patients receiving high dose corticosteroid therapy. Glucocorticoids cause hyperglycemia by inducing insulin resistance, increasing liver gluconeogenesis, and impairing pancreatic β-cell function [35, 36].

b.*Beta agonist medications and other catecholamines*: Several animal and human studies have demonstrated that B2-agonists can affect glucose levels by altering pancreatic insulin secretion, liver metabolism, and glucose uptake [37]. The overall result is hyperglycemia, which can be clinically significant in patients with AECOPD, since many of these patients take corticosteroids, have sedentary lifestyles, and are overweight. Studies have shown that catecholamines lead to hyperglycemia directly by affecting the pancreas, by increasing glucagon secretion, or by exerting a direct effect independent of pancreatic hormone release[38, 39].

c. *Antibiotics*: Several antibiotics have been reported to cause abnormalities in glucose metabolism and can cause both hyperglycemia and hypoglycemia. Fluoroquinolones are the only antibiotics consistently associated with hyperglycemia[40]. A large cohort with 78, 433 diabetic patients were followed over a 23 month period to determine the relative risk of hyperglycemia and hypoglycemia in association with antibiotic treatment. The absolute risk for hyperglycemia was 1.6 per 1000 persons for macrolides, 2.1 for cephalosporins, 6.9 for moxifloxacin, 3.9 for levofloxacin, and 4.0 for ciprofloxacin. The adjusted odds ratios for fluoroquinolones compared to macrolides were 2.48 for moxifloxacin, 1.75 for levofloxacin, and 1.87 for ciprofloxacin[41].Yamada, et al. showed that chronic treatment with gatifloxacin decreases islet insulin content by inhibiting insulin biosynthesis [42]. Park Wyllie, et al. studied 470 patients treated for hyperglycemia within 30 days after antibiotic therapy and found that gatifloxacin was associated with an increased risk of hyperglycemia (adjusted odds ratio, 16.7; 95 % confidence interval, 10.4 to 26.8) [43].

d. *Theophylline*: In an animal study, aminophylline administration caused hyperglycemia possibly by the induction of insulin resistance[44]. Another study with preterm infants showed that plasma glucose levels increased after theophylline therapy was started in infants with respiratory problems[45].

Effect of hyperglycemia on inflammatory cell responses, the immune system, and tissue injury

Diabetes mellitus, hyperglycemia, and impaired glucose tolerance are associated with increased C-reactive protein, interleukin-6, and tumor necrosis factor-α [46]. Yorek, et al. studied the pro-inflammatory effect of glucose in vitro and showed that incubation of endothelial cells in high glucose concentrations results in radical oxygen species production and activation of the transcription factor nuclear factor-kappa B and an increase in monocyte adhesion [47]. Glucose levels have regulatory effects on some pro-inflammatory cytokines [48]. Interestingly, these cytokines (IL-6, IL-18, and TNF-α) have been implicated in the development of insulin resistance, atherosclerotic plaque rupture, and future cardiovascular events, and this could explain the association between hyperglycemia and cardiovascular events[49].

Several studies have concluded that hyperglycemia can alter cellular defense mechanisms during infection. High glucose levels alter the immune system by decreasing neutrophil degranulation during inflammation, by causing defects in adherence[50], and by impairing phagocytosis[51], chemotaxis [52], bacterial killing, and the respiratory burst [53]. Hyperglycemia can also reduce protease secretion by neutrophils, leading to decreases in antimicrobial activity [54]. Turina, et al concluded that short term hyperglycemia affects all major components of innate immunity and impairs the ability of the host to control infection [55]. Von Kanel reported that a short term rise in blood glucose levels in normal individuals can lead to a decrease in the number of lymphocytes and cause redistribution in lymphocytes subsets [56]. These abnormalities are reversed when glucose is lowered [57]. A recent review suggested an association between diabetes and a decreased risk of lung injury, possibly mediated by reduced inflammatory responses secondary to hyperglycemia [58].

Management of hyperglycemia during acute COPD exacerbations

Hyperglycemia is a common problem in hospitalized patients and can be both a difficult and costly problem during patient care. Observational and randomized controlled studies suggest that good glycemic control in hospitalized patients improves outcomes in both medical and surgical patients. The Endocrine Society, the American Diabetes Association, the American Heart Association, the American Association of Diabetes Educators, the European Society of Endocrinology, and the Society of Hospital Medicine conducted a group meeting to formulate evidence-based practice guidelines for the management of hyperglycemia in hospitalized patients in the non-critical care setting. The following is a brief summary of their recommendations [59].

1. *Diagnosis of hyperglycemia and diabetes mellitus in hospitalized patients*:

- Assess all admitted patients for a history of diabetes.
- Measure glucose in all admitted patients, regardless of a prior diagnosis of diabetes.
- Use point of care testing on any patient with blood glucose >140 mg/dl.
- Use point of care testing for 24-48 hours on patients receiving treatment, like corticosteroids, known to cause hyperglycemia.
- Measure Hb A1C for diabetic patients and patients with glucose levels >140 mg/dl.

2. *Monitoring blood glucose levels:* Use point of care blood capillary testing with accurate devices, and time the glucose readings according to the patient's nutritional intake and medication schedules.

3. *Glucose level targets*: Aim for a premeal glucose level less than 140 mg/dl and random levels less than 180 mg/dl. However, these numbers should be adjusted according to the patient`s clinical situation. For example, allow glucose levels up to 200 mg/dl for terminally ill patients or patients with a high risk for hypoglycemia. To avoid hypoglycemia, patients with glucose values below 100 mg/dl should have their antidiabetic regimens modified.

4.*Management of hyperglycemia*: Nutritional therapy should be included as a component of the glycemic management program, and patients shall receive a consistent amount of carbohydrates with each meal. Oral hypoglycemic agents should be stopped, and insulin therapy should be started as the preferred method to achieve good glycemic control.

5. *Special situations:*

- Subcutaneous insulin should be started at least 1-2 hours before stopping insulin infusion.
- Patients receiving parenteral or enteral nutrition should have bedside point of care testing. It can be stopped in patients with no prior history of DM and with glucose levels < 140 mg/dl.
- Perioperative glucose control is important.
- Patients receiving glucocorticoids therapy need bedside point of care monitoring of the glucose levels.

6. *Hypoglycemia*: Prompt recognition and treatment are crucial.

7. *Glycemic control program*: Start in the hospital.

8. *Education:* Patient and professional education on diabetes management and avoidance of hypoglycemia.

The management of blood glucose levels in critical care settings is a controversial topic with several randomized controlled trials comparing "tight" to "loose" blood glucose control. The large international randomized controlled trial ("the NICE-SUGAR Study") demonstrated target blood glucose of less than 180 mg/dl resulted in lower mortality than a target of 81 to 108 mg/dl in critical care units [60].

Discussion

In this review, we have discussed studies that suggest a relationship between hyperglycemia and poor outcomes in AECOPD. However, these studies do not completely explain the pathophysiology underlying these complications. Also, one study failed to find a relationship between hyperglycemia in patients with AECOPD and reported that hypoglycemia was associated with poor outcomes. Other studies have reported poor outcomes in patients with diabetes mellitus and hyperglycemia who are admitted for different medical conditions, such as myocardial infarction[61] and cerebrovascular accidents[62, 63]. Krinsley studied the relationship between hyperglycemia and hospital mortality in a heterogeneous group of critically ill patients and concluded that even modest hyperglycemia after intensive care unit admission was associated with a substantial increase in hospital mortality in patients with a wide range of medical and surgical diagnoses[64]. Animal model studies and other observational studies suggest that possible mechanisms include defective immune responses and an increased risk

of infection, increased thrombotic events, increased oxidative stress, and increased inflammatory markers [65]. Several studies have shown that hyperglycemia is associated with increased numbers of pathogens and MRSA colonization of the sputum.

Conclusion

Hyperglycemia has been associated with increased morbidity, increased mortality, and longer lengths of stay, and more hospital costs in patients with both medical and surgical conditions. AECOPD is associated with hyperglycemia due to the stress related hormonal response to acute illness and possibly some of the medications routinely used in the treatment of AECOPD. Several studies suggest that hyperglycemia has adverse outcomes in patients with AECOPD, but the pathophysiology underlying these effects has not been determined. We need more research on outcomes in AECOPD in patients with hyperglycemia, using larger sample sizes and taking into consideration a design which can control for cofounders and provide more insight into the pathophysiology. In addition, a study on targeted glycemic control and outcomes is needed.

Key points

1. Clinical studies have shown that hyperglycemia is associated with adverse outcomes in hospitalized patients in general medical and surgical wards and in critical care units.
2. Studies have associated hyperglycemia in AECOPD with increased morbidity, mortality, and length of stay.
3. The pathogenesis underlying these adverse outcomes may include decreases in the immune responses to infection, increased susceptibility to infection, and increased tissue injury.
4. The timing and number of glucose measurements used to characterize the hyperglycemia in these studies have been variable. More consistent glucose measurements, including late afternoon and early evening, might identify associations better.
5. A single study found a correlation between hypoglycemia and poor outcomes. This result might suggest that hypoglycemia indicates a failure of the normal body response to stress which leads to adverse outcomes.
6. The management of hyperglycemia associated with hospitalization requires both detection and treatment. Insulin is the preferred drug for treatment.

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Table Summery of the studies investigating the relationship between blood glucose level and COPD exacerbation outcomes

Author, Date	Number of patients	Glucose measurement (initial, mean, peak, etc.)	Outcomes	Author conclusions
Baker, 2006	284 AECOPD	The highest blood glucose recorded was used in the analysis.	The risk of adverse outcomes increased with increasing hyperglycemia; isolation of multiple pathogens and *Staphylococcus aureus* from sputum increased	Increasing blood glucose concentrations are associated with adverse clinical outcomes in patients with AECOPD.
Chakrabarti, 2009	88 AECOPD	Random blood glucose levels were measured before the initiation of NIV	The combination of baseline respiratory rate <30 breaths/min and random glucose <7 mmol/l increased prediction of NIV success to 97%	In acute decompensated ventilatory failure complicating COPD, hyperglycemia upon presentation was associated with a poor outcome.
Moretti, 2000	155 AECOPD	Fasting blood glucose levels	The occurrence of "late NIMV failure" was significantly associated with functional daily life limitations and medical complications, such as hyperglycemia and a low pH.	After the initial success of NIMV, a significant subset of patients (>20%) may have a new episode of acute respiratory failure resulting from new complications.
Kasirye, 2013	209 AECOPD	Daily mean blood glucose levels	Lower blood glucose and age were the most significant risk factors for in-hospital complications	Hypoglycemia results in higher risk for in-hospital complication and longer length of stay.
Burt, 2013	47 AECOPD	Mean glucose levels assessed by CGMS	Length of hospital stays increased by 10% for each mmol/L increase in mean glucose	Mean glucose was independently associated with increase length of hospital stay.
Parappil, 2010	172, including 39 with DM, AECOPD	Patients with diagnoses of DM.	A non-significant trend for increased length of stay and deaths in those with diabetes compared with non-diabetic patients	DM prolongs length of stay and increases risk of death in patients with AECOPD.

AECOPD-acute exacerbation of chronic obstructive pulmonary disease; DM-diabetes mellitus; NIV-noninvasive ventilation; CGMS-continuous glucose monitoring system

References

1. Evensen AE. Management of COPD exacerbation. Am Fam Physician 2010; 81(5):607-613.

2. Patil SP, Krishnan JA, Lechtzin N, Dinette GB. In-hospital mortality following acute exacerbations of chronic obstructive pulmonary disease. Arch Intern Med 2003; 163(10):1180-1186.

3. McAlister FA, Majumdar SR, Blitz S, et al. The relation between hyperglycemia and outcomes in 2,471 patients admitted to the hospital with community-acquired pneumonia. Diabetes Care 2005; 28(4):810–5.

4. Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 2000; 4;355(9206):773-8.

5. Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke 2001; 32(10):2426-32.

6. Butler SO, Btaiche IF, Alaniz C. The relationship between hyperglycemia and infection in critically ill patients; Glucose metabolism in critical illness. Pharmacother 2005; 25(7):963-976.

7. Baker EH, Janaway CH, Philips BJ, et al. Hyperglycemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. Thorax 2006; 61(4):284-9.

8. Chakrabarti B, Angus RM, Agarwal S, Lane S, Calverley PM. Hyperglycemia as a predictor of outcome during non-invasive ventilation in decompensated COPD. Thorax 2009; 64(10):857-62.

9. Moretti M, Cilione C, Tampieri A, Fracchia C, Marchioni A, Nava S. Incidence and causes of non-invasive mechanical ventilation failure after initial success. Thorax 2000; 55(10): 819–825.

10. Burt MG, Roberts GW, Aguilar-Loza NR, Quinn SJ, Frith PA, Stranks SN. Relationship between glycaemia and length of hospital stay during acute exacerbation of chronic obstructive pulmonary disease. Int Med Jour 2013; 43(6):721-724.

11. Parappil A, Depxynski B, Collett P, et al. Effect of comorbid diabetes on length of stay and risk of death in patients admitted with acute exacerbations of COPD. Respirology 2010; 15(6):918-22.

12. Kasirye Y, Simpson M, Mamillapalli CK, Epperla N, Liang H, Yale SH. Association between blood glucose level and outcomes in patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease. WMJ 2013; 112(6):244-9.

13. Chung KF. Cytokines in chronic obstructive pulmonary disease. Eur Respir J Suppl 2001;34(18):50s-59s

14. Burt MG, Roberts GW, Aguilar-Loza NR, Frith P, Stranks SN. Continuous monitoring of circadian glycemic patterns in patients receiving prednisone for COPD. J Clin Endocrinol Metab 2011; 96(6):1789-1796.

15. Godar DA, Kumar DR, Schmelzer KM, et al. The impact of serum glucose on clinical outcomes in patients hospitalized with community-acquired pneumonia. WMJ 2011; 110(1):14-20.

16. Arabi YM, Tamim HM, Rishu AH. Hypoglycemia with intensive insulin therapy in critically ill patients: predisposing factors and association with mortality. Crit Care Med 2009; 37(9):2536-2544.

17. Philips BJ, Redman J, Brennan A, Wood D, Holliman R, Baines D, Baker EH. Glucose in bronchial aspirates increases the risk of respiratory MRSA in intubated patients. Thorax 2005; 60(9):761-4.

18. Baker EH, Wood DM, Brennan AL, et al. Hyperglycemia and pulmonary infection. Proc Nutr Soc 2006; 65(3):227-35.

19. Umpierrez GE, Isaacs SD, Bazargan H, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metabol 2002; 87(3):978-82.

20. Rana JS, Mittleman MA, Sheikh J, Hu FB, Manson JE, Colditz GA, Speizer FE, Barr RG, Camargo CA Jr. Chronic obstructive pulmonary disease, asthma, and risk of type 2 diabetes in women. Diabetes Care. 2004; 27(10):2478-84.

21. Archer JRH, EH. Diabetes and metabolic dysfunction in COPD. Respiratory Med: COPD update.2009; 5: 67–74.

22. Breyer MK, Rutten EP, Locantore NW, Watkins ML, Miller BE, Wouters EF. Dysregulated adipokine metabolism in chronic obstructive pulmonary disease. Eur J Clin Invest 2012; 42(9):983-91.

23. McGuinness OP. Defective glucose homeostasis during infection. Ann Rev Nutr 2005; 25:9-35.

24. Rolih CA, Ober KP. The endocrine response to critical illness. Med Clin North America 1995; 79(1):211–224.

25. Kuhn CM, Cochrane C, Feinglos MN, Surwit RS. Exaggerated peripheral responses to catecholamines contributes to stress-induced hyperglycemia in the ob/ob mouse. Pharmacology Biochem Behavior1987; 26(3):491–495

26. Oltmanns KM, Gehring H, Rudolf S, Schultes B, Rook S, Schweiger U, Born J, Fehm HL, Peters A. Hypoxia causes glucose intolerance in humans. Am J Respir Crit Care Med 2004; 169(11):1231-1237.

27. Polotsky VY, Li J, Punjabi NM, Rubin AE, Smith PL, Schwartz AR, O'Donnell CP. Intermittent hypoxia increases insulin resistance in genetically obese mice. J Physiol 2003; 552(1):253-64.

28. Iiyori N, Alonso LC, Li J, Sanders MH, Garcia-Ocana A, O'Doherty RM, Polotsky VY, O'Donnell CP. Intermittent hypoxia causes insulin resistance in lean mice independent of autonomic activity. Am J Respir Crit Care Med 2007; 175(8): 851–857.

29. Louis M, Punjabi NM. Effects of acute intermittent hypoxia on glucose metabolism in awake healthy volunteers. J Applied Physiol 2008; 106(5): 1538-1544.
30. Pallayova M, Lazurova I, Donic V: Hypoxic damage to pancreatic beta cells–the hidden link between sleep apnea and diabetes. Med Hypotheses 2011; 77(5):930–934.
31. Cheng N, Cai W, Jiang M, Wu S. Effect of hypoxia on blood glucose, hormones, and insulin receptor functions in newborn calves. Pediatr Res 1997; 41(6): 852–856.
32. Adrogue HJ, Chap Z, Okuda Y et al. Acidosis-induced glucose intolerance is not prevented by adrenergic blockade. Am J Physiol 1988; 255 (6 Pt 1): E812–23.
33. Bigner DR, Goff JP, Faust MA, Burton JL, Tyler HD, Horst RL. Acidosis effects on insulin response during glucose tolerance tests in Jersey cows. J Dairy Sci 1996; 79(12):2182-8.
34. Donihi AC, Raval D, Saul M, Korytkowski MT, DeVita MA. Prevalence and predictors of corticosteroid-related hyperglycemia in hospitalized patients. Endocr Pract 2006; 12(4):358-62.
35. Patel R, Patel M, Tsai R, Lin V, Bookout AL, Zhang Y, Magomedova L, Li T, Chan JF, Budd C, Mangelsdorf DJ, Cummins CL. LXRβ is required for glucocorticoid-induced hyperglycemia and hepatosteatosis in mice. J Clin Invest 2011(1); 121:431–441.
36. Van Raalte DH, Nofrate V, Bunck MC, Van Lersel T, Nasander UK, Heine RJ, Mari A, Dokter WHA, Diamant M. Acute and 2-week exposure to prednisolone impair different aspects of beta-cell function in healthy men. Eur J Endocrinol 2010; 162(4):729–735.
37. Philipson LH. Beta-agonists and metabolism. J Allergy Clin Immunol 2002; 110(6):S3137.
38. Gerich JE, Lorenzi M, Tsalikian E, Karam JH. Studies on the mechanism of epinephrine-induced hyperglycemia in man. Evidence for participation of pancreatic glucagon secretion. Diabetes 1976; 25(1):65-71.
39. Woodson LC, Bee DE, Potter DE. Catecholamine-induced hyperglycemia in dogs: independence from alterations in pancreatic hormone release. Horm Metab Res 1980; 12(9):434-9.
40. Rehman A, Stephen M. Setter SM, Vue MH. Drug-induced glucose alterations part 2: drug-induced hyperglycemia. Diabetes Spectrum 2011; 24(4): 234-238.
41. Chou HW, Wang JL, Chang CH, Lee JJ, Shau WY, Lai MS. Risk of severe dysglycemia among diabetic patients receiving levofloxacin, ciprofloxacin, or moxifloxacin in Taiwan. Clin Infect Dis 2013; 57(7):971-80.
42. Yamada C, Nagashima K, Takahashi A, Ueno H, Kawasaki Y, Yamada Y, Seino Y. Gatifloxacin acutely stimulates insulin secretion and chronically suppresses insulin biosynthesis. Eur J Pharmacol 2006; 553(1-3):67-72.
43. ParkWyllie LY, Juurlink DN, Kopp A, Shah BR, Stukel TA, Stumpo C, Dresser L,Low DE, Mamdani MM: Outpatient gatifloxacin therapy and dysglycemia in older adults. N Engl J Med 2006; 354(13):1352–1361.
44. Sacca L, Perez G, Rengo F, Pascucci I, Condorelli BS, Condorelli M. Effects of theophylline on glucose kinetics in normal and sympathectomized rats. Diabetes 1975; 24(3):249-56.
45. Diderholm B, Ewald U, Gustafsson J. Effect of theophylline on glucose production and lipolysis in preterm infants (< or = 32 weeks). Pediatr Res1999; 45(5 Pt 1):674-9.
46. De Rekeneire N, et al. Diabetes, Hyperglycemia, and Inflammation in Older Individuals, the health, aging and body composition study. Diabetes Care 2006; 29(8):1902-8.
47. Yorek MA, Dunlap JA. Effect of increased concentration of D-glucose or L-fucose on monocyte adhesion to endothelial cell monolayers and activation of nuclear factor-kappaB. Metabolism 2002; 51(2):225-34.
48. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliaro L, Ceriello A, Giugliano D. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation 2002; 106(16):2067–2072.
49. Esposito K, Marfella R, Giugliano D. Stress hyperglycemia, inflammation, and cardiovascular events. Diabetes Care 2003; 26(5):1650-1651.
50. Bagdade JD, Stewart M, Walters E. Impaired granulocyte adherence. A reversible defect in host defense in patients with poorly controlled diabetes. Diabetes 1978; 27(6):677–681.
51. Van Oss CJ, Border JR. Influence of intermittent hyperglycemic glucose levels on the phagocytosis of microorganisms by human granulocytes in vitro. Immunol Commun 1978; 7(6):669–676.
52. Mowat A, Baum J. Chemotaxis of polymorphonuclear leukocytes from patients with diabetes mellitus. N Engl J Med 1971; 284(12):621–627.
53. Alexiewicz J, Kumar D, Smogorzewski M, Klin M, Massry S. Polymorphonuclear leukocytes in non-insulin-dependent diabetes mellitus: abnormalities in metabolism and function. Ann Intern Med 1995; 123(12):919–924.
54. Stegenga ME, van der Crabben SN, Blümer RM, Levi M, Meijers JC, Serlie MJ, Tanck MW, Sauerwein HP, van der Poll T. Hyperglycemia enhances coagulation and reduces neutrophil degranulation, whereas hyperinsulinemia inhibits fibrinolysis during human endotoxemia. Blood 2008; 112(1):82-9.
55. Turina M, Fry DE, Polk HC Jr. Acute hyperglycemia and the innate immune system, clinical, cellular and molecular aspect Crit Care Med 2005; 33(7):1624-33.
56. Von Kanel R, Mills P, Dimsdale J. Short-term hyperglycemia induces lymphopenia and lymphocyte subset redistribution. Life Sciences 2001; 699(3):255–262.
57. Bouter KP, Meyling FH, Hoekstra JB, Masurel N,

Erkelens DW, Diepersloot RJ. Influence of blood glucose levels on peripheral lymphocytes in patients with diabetes mellitus. Diabet Med 1992; 9(1):66-9.

58. Honiden S, Gong MN. Diabetes, insulin and development of acute lung injury. Crit Care Med 2009; 37(8): 2455–2464.

59. Umpierrez GE, Hellman R, Korytkowski MT, Kosiborod M, Maynard GA, Montori VM, Seley JJ, Van den Berghe G. Management of hyperglycemia in hospitalized patients in non-critical care setting: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metabol 2012; 97 (1):16–38.

60. The NICE-SUGAR study investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009; 360:1283-1297.

61. Kersten J, Toller W, Tessmer J, Pagel P, Warltier D. Hyperglycemia reduces coronary collateral blood flow through a nitric oxide-mediated mechanism. Am J Physiol 2001; 281(5):H2097–H2104.

62. Pulsinelli WA, Waldman S, Rawlinson D, Plum F. Moderate hyperglycemia augments ischemic brain damage: a neuropathologic study in the rat. Neurology 1982; 329(11):1239–1246.

63. Prado R, Ginsberg MD, Dietrich WD, Watson BD, Busto R. Hyperglycemia increases infarct size in collaterally perfused but not end-arterial vascular territories. J Cereb Blood Flow Metab 1988; 8(2):186–192.

64. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc 2003; 78(12):1471-148.

65. Clement S, et al. Management of diabetes and hyperglycemia in hospitals. Diabetes Care 2004; 27(2): 553-591.