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Diabetes, insulin, and development of acute lung injury

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Abstract

Objectives—Recently, many studies have investigated the immunomodulatory effects of insulin and glucose control in critical illness. This review examines evidence regarding the relationship between diabetes and the development of acute lung injury/acute respiratory distress syndrome (ALI/ARDS), reviews studies of lung injury related to glycemic and nonglycemic metabolic features of diabetes, and examines the effect of diabetic therapies.

Data Sources and Study Selection—A MEDLINE/PubMed search from inception to August 1, 2008, was conducted using the search terms acute lung injury, acute respiratory distress syndrome, hyperglycemia, diabetes mellitus, insulin, hydroxymethylglutaryl-CoA reductase inhibitors (statins), angiotensin-converting enzyme inhibitor, and *peroxisome proliferator-activated receptors*, including combinations of these terms. Bibliographies of retrieved articles were manually reviewed.

Data Extraction and Synthesis—Available studies were critically reviewed, and data were extracted with special attention to the human and animal studies that explored a) diabetes and ALI; b) hyperglycemia and ALI; c) metabolic nonhyperglycemic features of diabetes and ALI; and d) diabetic therapies and ALI.

Conclusions—Clinical and experimental data indicate that diabetes is protective against the development of ALI/ARDS. The pathways involved are complex and likely include effects of hyperglycemia on the inflammatory response, metabolic abnormalities in diabetes, and the interactions of therapeutic agents given to diabetic patients. Multidisciplinary, multifaceted studies, involving both animal models and clinical and molecular epidemiology techniques, are essential.

Keywords

acute respiratory distress syndrome; acute lung injury; hyperglycemia; diabetes mellitus; insulin

Acute lung injury/acute respiratory distress syndrome (ALI/ARDS) is a devastating condition defined by the American-European Consensus Committee on ARDS as an acute syndrome of lung inflammation and increased permeability associated with severe hypoxia and bilateral infiltrates on chest radiographs with no evidence of left heart failure (1). Decades of animal and clinical studies have identified several pathophysiologic mechanisms important in the development of ALI/ARDS. Acute inflammation is a key feature, as evidenced by the central role of neutrophil recruitment and activation and the increased expression and release of inflammatory mediators, such as proinflammatory and anti-inflammatory cytokines and chemokines. Disturbances in surfactant function and edema

clearance are present, and ample evidence supports imbalances in oxidant/antioxidant activity (2), coagulation/fibrinolysis, and fibrosis/repair. The relative balance of these interacting pathways either exacerbates or ameliorates further lung injury (3,4).

ALI/ARDS is a commonly encountered condition, with 190,600 cases of ALI per year in the United States and an associated 74,500 deaths and 3.6 million hospital days (5). Of the predisposing injuries for ALI/ARDS, sepsis is associated with the highest risk for progression into ALI/ARDS, at a rate of 40% (6). Yet most patients with sepsis do not develop ARDS. Our current understanding of who is most likely to develop lung injury and why is incomplete. One of the patient-based clinical factors shown to be an important predictor for ALI/ARDS in multiple studies is a history of diabetes mellitus, which appears to be protective against the development of ALI/ARDS. However, the mechanisms underlying the association between diabetes and ALI/ARDS are not clear.

Several recent clinical trials have examined the use of intensive insulin therapy in the intensive care unit (ICU) (7-11). Although none of the available trials have specifically examined the outcome of ALI/ARDS with insulin therapy, these trials have stimulated much research and have provided insights into how diabetes, insulin, and glucose control may play a role in inflammation in critical illnesses, such as ALI/ARDS.

In the following sections, we review clinical and animal studies in which diabetes was shown to be important in the development of ALI/ARDS. We explore how hyperglycemia and the nonglycemic metabolic features of diabetes may be relevant in ALI/ARDS. Finally, we discuss the possible effects of diabetic therapy on the development of lung injury, with a focus on the potential role of insulin in lung injury.

METHODS

We performed a comprehensive search on MEDLINE/PubMed restricted to the English language from inception to August 1, 2008. We used the search terms acute lung injury (ALI), acute respiratory distress syndrome (ARDS), hyperglycemia, diabetes mellitus, insulin, hydroxymethylglutaryl-CoA reductase inhibitors (statins), angiotensin-converting enzyme inhibitor (ACE)-I, peroxisome proliferator-activated receptors (PPAR), and combinations of these terms. In addition, we manually searched the bibliographies of retrieved articles for completeness. All publication types were included. This study was exempt from approval by the local institutional review board.

RESULTS AND DISCUSSION

Diabetes and Acute Lung Injury

Clinical Studies—A history of diabetes has been shown to predict greater susceptibility to or worse outcomes with acute renal failure and trauma (12,13). In contrast to this, a large, prospective, multicenter study of patients with septic shock found diabetes to be protective against the development of ALI. Diabetic patients developed ARDS less often than nondiabetic patients (25% vs. 47%; $p = .03$) (14,15). This protective association was confirmed in a larger cohort of 688 critically ill patients at risk for ARDS from sepsis, trauma, massive transfusion, and aspiration. Diabetes was protective against the development of ARDS even after adjustment for potential confounders, such as age, clinical risk for ARDS, severity of illness, and transfusion (adjusted odds ratio 0.58; 95% confidence interval, 0.36-0.92) (16). Recently, this finding was reconfirmed and validated in a third independent cohort of patients with sepsis, in which diabetes was found in 24% of patients who developed ALI compared with 43% of patients without ALI ($p = .012$) (17). In these three independent cohorts of critically ill patients with common risks factors for ALI/ARDS,

the odds ratio for diabetes and ALI/ARDS ranged from 0.33 to 0.58 after adjustment for potential confounders, such as age, gender, pneumonia, and severity of illness (Fig. 1 and Table 1).

Experimental Animal Studies—The clinical observation that diabetes is protective against the development of ALI/ARDS has led to experimental studies of ALI in various models of type 1 and type 2 diabetes. Compared with nondiabetic rats, alloxan-treated rats (a model of type 1 diabetes) demonstrate less lung injury after aerosolized or intratracheal instillation of endotoxin characterized by decreased neutrophils in the bronchoalveolar fluid (BAL); reduced superoxide generation; lower BAL concentrations of inflammatory cytokines, such as tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , and IL-10; and blunted increase in neutrophil arachidonic acid and BAL prostaglandin E₂ (18-20).

Similar results were seen in animal models of type 2 diabetes. Type 2 diabetic Zucker rats exhibited substantially less microvascular protein extravasation after intratracheal instillation of lipopolysaccharide (LPS) compared with nondiabetic rats (21). Because of leptin resistance caused by a defective leptin receptor, the *db/db* mice have the phenotype of hyperglycemia, obesity, and dyslipidemia and are another model of type 2 diabetes. In one recent study, the diabetic *db/db* mice were protected from hyperoxia-induced acute lung injury with less interstitial edema on histology, lower pathologic injury scores, less increase in lung permeability, lower levels of BAL IL-6 and TNF- α , and better survival (22,23).

These animal models of diabetes and lung injury support the clinical observation that diabetes may protect against the development of ALI/ARDS. However, the mechanisms behind the effect of diabetes on ALI/ARDS are unclear. Certainly, hyperglycemia is a key feature of diabetes, but the majority of patients with diabetes have type 2 diabetes with additional features of the metabolic syndrome, including insulin resistance, obesity, and dyslipidemia. Recent studies provide insights into the potential links between ALI and the glycemic and nonglycemic features of diabetes.

Hyperglycemia and ALI/ARDS

Because hyperglycemia is a central feature in diabetes, one logical question is whether hyperglycemia is also associated with decreased ALI development. The clinical and experimental data on hyperglycemia and lung injury are conflicting, and there is no clear evidence to suggest that acute hyperglycemia alone can account for the protective association between diabetes and the development of ALI/ARDS.

Clinical Studies—In Moss and colleagues' (14) multicenter study of sepsis, where the protective association between diabetes and ALI was first noted, glucose was higher among patients who did not develop ALI/ARDS (Table 1), but on multivariate analyses this was not significant. In a more recent study, higher glucose levels within the first 24 hrs of respiratory failure were associated with a decreased risk of developing ALI/ARDS ($p = .025$), but presence of diabetes was not examined (24). On the other hand, in the Molecular Epidemiology of ARDS Study, the peak glucose at admission to the ICU was higher among patients with diabetes compared with those patients without diabetes ($p < .0001$) and among nonsurvivors compared with survivors ($p = .002$). But there was no difference in peak glucose between critically ill patients who developed ARDS compared with non-ARDS patients (median 186 mg/dL, [25% to 75%] 148-250 in ARDS vs. 178 mg/dL [25% to 75%] 142-237 in non-ARDS; $p = .1$) (25).

A number of other studies have shown hyperglycemia to exacerbate inflammation and promote injury. In clinical studies, acute hyperglycemia was associated with increased production of inflammatory cytokines and increased mortality rate in critically ill patients,

independent of diabetes (26,27). Hyperglycemia is a risk factor for increased development of ALI in specific disease states, such as *Enterovirus* infection (28), Coxsackievirus infection (29), and Japanese B encephalitis (30).

Experimental Animal Studies—It is also not clear from experimental data whether hyperglycemia would ameliorate or exacerbate the intense inflammation seen in ALI/ARDS. Hyperglycemia has been shown to have immunomodulatory effects marked by increased production of anti-inflammatory cytokines like IL-10, promotion of mitochondrial dysfunction (31), and impairment of neutrophil function resulting in decreased intracellular bactericidal activity, opsonic activity, and innate immunity (32-35). Such effects could theoretically modulate the intense inflammation seen in ALI/ARDS.

On the other hand, hyperglycemia can promote inflammation by increasing proinflammatory cytokines, such as TNF- α , IL-1 β , IL-6, IL-8, and IL-18 (36); increasing leukocyte adhesion molecules; inducing nuclear factor- κ B (37); and promoting the procoagulant state (32-35). Although glucose was shown to have the capacity to act as a hydroxyl radical scavenger *in vivo* historically (38), it is now well established that hyperglycemia leads to significant oxidative stress, which could enhance the oxidative injury seen in ALI/ARDS (39-41). Consistent with these other studies, an intravenous LPS model of ALI recently showed hyperglycemia to exacerbate lung injury (42).

Furthermore, the hyperglycemic state induces formation of advanced glycation end products (AGE), which is now recognized to promote inflammation and endothelial dysfunction (43). Interaction of AGE and receptors for AGE (RAGE) has been implicated in the development of lung fibrosis in bleomycin lung injury (44), is involved in endotoxin-induced ALI (45), and modulates outcomes in septic shock (46). Although AGEs can be difficult to measure experimentally, RAGE has recently been shown to be a marker of type I cell injury in ALI (47). Additionally, a study published by the ARDS Network demonstrated that higher circulating levels of RAGE were associated with severity of lung injury and clinical outcomes (48). Finally, RAGE has multiple ligands and binds not only AGEs but also to proinflammatory, calcium-binding S100 proteins (also known as calgranulins) and high-mobility group box-1 protein (42,49-52). It is unclear which of these ligands are most biologically relevant, *in vivo*, in pathologic states.

Metabolic Nonhyperglycemic Features of Diabetes and ALI/ARDS

Diabetes is characterized by more than hyperglycemia alone. The majority of diabetic patients around the world have type 2 diabetes with features of the metabolic syndrome, including insulin resistance, obesity, and dyslipidemia. Recent *in vivo* and *in vitro* experimental studies provide insights into the potential links between ALI and the metabolic syndrome, suggesting possible nonglycemic mechanisms by which diabetes may facilitate or protect against the development of lung injury.

One example of the nonglycemic link between diabetes and lung injury involves the peroxisome proliferator-activated receptor (PPAR)- γ . PPAR- γ is important in the regulation of genes involved in lipid and glucose metabolism, insulin sensitivity, and adipogenesis (53,54). Although the effect is likely to be modulated by environmental and other genetic factors, the *Pro* allele of the *Pro12Ala* polymorphism in the *PPAR- γ* gene has been associated with increased receptor activity and increased risk of type 2 diabetes and insulin resistance in multiple replicated studies (55-58). Additionally, PPAR- γ seems to function as an important antiinflammatory agent that is highly expressed in neutrophils and alveolar macrophages and can decrease nicotinamide adenine dinucleotide phosphate oxidase activity, proinflammatory cytokines such as TNF- α and IL-12, inducible nitric oxide synthase expression, and production of matrix metalloproteinase-9; directly inhibit

neutrophil function (59); and influence levels of the decoy receptor soluble RAGE, which inhibits the inflammatory effects mediated by RAGE (60).

Lately, PPAR- γ and another subtype of PPAR (PPAR- α) were shown to have an important role in reducing lung injury associated with systemic inflammation and shock (61,62). Decreased expression of PPAR- γ messenger RNA has been found in lung tissue after acute hyperoxia or endotoxin-induced lung injury (63,64). Treatment with rosiglitazone, a PPAR- γ agonist, significantly limits the extent of lung injury in various animal models of ALI. PPAR- α knockout mice have enhanced histologic lung injury, neutrophil recruitment, and expression of proinflammatory cytokines like TNF- α and IL-1 after carrageenan-induced pleurisy or bleomycin-induced lung injury, whereas treatment of wild-type mice with a PPAR- α agonist significantly decreased lung injury (65,66).

Another example of a nonglycemic link between diabetes and lung injury is insulin-like growth factor (IGF)-1. Multiple endothelial specific growth factors, such as the keratinocyte growth factor and hepatocyte growth factor, are critical in lung inflammation and repair (67). Most recently, IGF-1 was found to be important in ALI/ARDS. IGF-1 belongs to a family of ligands important in growth, development, cell differentiation, and metabolism (68). When not bound to IGF-binding protein-3, IGF-1 binds to insulin receptors and to IGF-1 receptors with insulin-like effects and can improve insulin sensitivity and glucose control in diabetes (69-71). Low circulating levels of IGF-1 are seen in type 2 diabetes (72). In lung injury states, however, exuberant IGF-1 production appears to have deleterious effects. Using shotgun proteomics, investigators identified IGF-1 and IGF-binding protein-3 as important in the pathogenesis of ALI/ARDS, perhaps by suppression of lung fibroblast apoptosis (73) or via alteration of cell proliferation and repair (74). This is in line with previously published observations that IGF-I levels are increased in the fibroproliferative stage of ARDS and that these levels correlate with extracellular matrix protein deposition and cellular proliferation (75). As a corollary, mice with IGF-1 receptor deficiency are protected against hyperoxia-induced lung injury (76), and the addition of IGF-1/IGF-1 receptor anti-bodies appears to temper alveolar epithelial cell proliferation and differentiation in rats exposed to hyperoxia (77). Therefore, the relatively low circulating levels of IGF-1 seen in diabetes may be an additional protective link between diabetes and ALI (69).

Diabetes Therapies and Acute Lung Injury

Although the studies reviewed so far suggest possible links between diabetes or the sequelae of diabetes and ALI/ARDS, it is also possible that diabetes is a confounder and that other factors associated with diabetes treatment or management are truly related to the variable risk of developing lung injury (Fig. 2). Therapies for diabetes may also modify any direct effects diabetes may have on ALI. Insulin is one of the most common medications used in the management of diabetes and is usually the only diabetic treatment that is continued during critical illness. Recently, much has been published on the effects of insulin on the critically ill patient with and without preexisting diabetes.

Insulin and Acute Lung Injury

There is now ample evidence to support the notion that the effects of insulin extend far beyond simple glycemic control. In animal and clinical studies of critical illness, insulin has been shown to be immunomodulatory. Independent of glycemic control, insulin has been shown to a) modulate inflammation via the mannose binding lectin pathway (78), nuclear factor- κ B (79), and through alternations in proinflammatory and anti-inflammatory cytokines, such as TNF- α , pre-B-cell enhancing factor, IL-10, and IL-6 (80-83); b) reduce free fatty acids (84) and reverse the state of dyslipidemia in critical illness (85); c) regulate

apoptosis (86,87); d) prevent endothelial dysfunction (88) and hypercoagulation (89); e) decrease neutrophil chemotaxis and leukocyte adhesion via reduction of intercellular adhesion molecule-1 and macrophage inhibiting factor (80,88); f) attenuate the catabolic state of critical illness (90,91); and g) prevent excessive nitric oxide, which may attenuate the oxidative stress seen in ALI (92). Almost all of these mechanisms have been implicated in the pathogenesis of ALI (Fig. 3) (3,93).

In clinical studies, intensive insulin therapy decreases mortality and/or morbidity rates for critically ill patients, especially among patients with prolonged ICU stays (7,8). The issue of ALI/ARDS was not specifically examined in these studies, although patients randomized to intensive insulin therapy spent a significantly shorter time on mechanical ventilation (7,8).

While we await further human studies to explore the interaction between insulin and lung injury, experimental studies suggest a potential benefit of insulin therapy in different models of ALI/ARDS. In a recent study, Donnelly and colleagues (94) demonstrated that administration of insulin attenuated the systemic inflammatory response and reduced lung injury. After trauma, rats developed spontaneous hyperglycemia and acute lung injury. Traumatized rats treated with insulin exhibited significantly less pulmonary edema and fewer neutrophils in the BAL fluid despite increased circulating neutrophils, suggesting reduced transmigration of activated neutrophils across the pulmonary endothelial barrier.

Similar results were seen in a rat model of intravenous LPS-induced ALI (95). Using a hyperinsulinemic euglycemic clamp in which escalating doses of insulin were given while maintaining euglycemia, insulin was found to reduce pulmonary interstitial edema, protein leakage, histologic lung injury scores, and LPS-induced hypotension in a dose-dependent manner, possibly via reduction in nitric oxide and free radical production. Increasing insulin dose correlated with lower exhaled nitric oxide, plasma nitrate/nitrite concentrations, and methyl guanidine, a marker of hydroxyl radical production. In a separate study using a similar rat model of LPS-induced ALI, insulin therapy significantly tempered lung damage likely via suppression of high-mobility group box-1 protein release and downstream activation of nuclear factor- κ B (42).

The studies just described were performed in nondiabetic animals. In diabetes, studies of ALI have been limited to animal models of type 1 diabetes with only one type of lung injury model. In an alloxan animal model of type 1 diabetes with intratracheal LPS-induced ALI, insulin corrected the abnormalities in neutrophil count and cytokine concentration in the BAL and increased the intercellular adhesion molecules on lung vessels (18-20).

However, it is difficult to know whether insulin may be detrimental or beneficial in diabetes. We now understand that the balance of proinflammatory and anti-inflammatory responses is important in the development and resolution of ALI. If diabetes is protective in ALI because of chronic antiinflammatory effects, then reversal of this by insulin may negate any beneficial effect of diabetes on ALI. Alternatively, if insulin reverses the chronic immunosuppressive effects of diabetes and restores the balance in inflammatory response that should be seen after direct pulmonary injury, such as pneumonia, then insulin may be potentially beneficial. More studies are needed to determine the context by which insulin is detrimental or beneficial in ALI. In addition, because the majority of diabetic patients in the ICU have type 2 diabetes, studies involving animal models of type 2 diabetes are needed to determine the effects of insulin in this setting.

Other Diabetic Therapies and Acute Lung Injury

Insulin is not the only diabetic treatment that may modulate the development of ALI (Table 2). Agonists of PPAR- γ , such as rosiglitazone, have been approved by the U.S. Food and

Drug Administration since 1999 for treatment of type 2 diabetes (96). In animal studies, rosiglitazone mitigates lung injury and multiorgan failure in acute pancreatitis (97), bleomycin-induced lung injury (98), intravenous endotoxin-induced lung injury (66,99), nonseptic shock with zymosan (100), burns (101), and acute hyperoxia (65). In these studies, rosiglitazone was shown to reduce histologic lung injury, lung edema, and neutrophil infiltration of the lungs (65,66,98-100). These findings were accompanied by a reduction in lipid peroxidation and oxidative injury; reversal of the increase in inflammatory cytokines and adhesion molecules, such as TNF- α , cytokine-induced chemoattractant-1, myeloperoxidase, and intracellular adhesion molecule-1; and attenuation in the production of nitric oxide. Simultaneous administration of an antagonist of PPAR- γ and rosiglitazone obliterates all of the protective effects of rosiglitazone and results in lung injury similar to that which occurs in untreated control animals (65,66,98-100). All of this suggests a potential role for PPAR- γ and PPAR- γ agonists in the development of ALI.

Other drugs commonly used in the management of diabetes may be important in the development of ALI. Metformin was recently shown to reduce severity of LPS-induced lung injury by modifying mitochondrially derived reactive oxygen species, thereby reducing oxidative injury (102).

Because of the high frequency of cardiovascular disease, diabetic patients are often treated with ACE inhibitors. Although ALI/ARDS was not specifically examined, clinical studies have found that prior use of ACE inhibitors was associated with a decreased risk of developing pneumonia in Asians (103). In Caucasians, ACE inhibitor use was protective against developing pneumonia only among diabetic patients, and ACE inhibitor use was associated with decreased mortality from community-acquired pneumonia (104-106). Interestingly, the variable findings with regard to ACE inhibitor use and risk of pneumonia between races may be attributable to the presence of an insertion polymorphism in intron 16 of the *ACE* gene (107), which has been previously associated with the development of and mortality in ALI/ARDS (108-110).

ACE inhibitors improve endothelial function in sepsis (111-113) and prevent development of pulmonary arterial hypertension and ARDS (114). In animal models, ACE inhibitors and/or angiotensin receptor blockers attenuate lung inflammation and apoptosis triggered by barotrauma (115) and reduce the fibroproliferative response after bleomycin-induced lung injury (116).

Diabetic patients are often treated with hydroxymethylglutaryl-CoA reductase inhibitors for their dyslipidemia. Recently, statin use was associated with decreased mortality rate in hospitalized patients with community-acquired pneumonia, a leading cause of ALI/ARDS (105). In a recent Irish cohort of patients with ALI/ARDS, statin use was associated with a nonsignificant trend toward lower mortality rate ($p = .09$) (117). Preliminary evidence from animal models of ALI suggests that hydroxymethylglutaryl-CoA reductase inhibitors, or statins, are capable of reducing vascular leak and inflammation (118-120).

Clinical Implications and Future Research Directions

More research is required to understand the role of diabetes, insulin, and hyperglycemia in critically ill patients with ALI. An improved understanding of diabetes, insulin, and ALI/ARDS has important clinical implications in the diagnosis, prevention, and management of ALI/ARDS. Given the increasing incidence of sepsis and diabetes and the aging of the population, a better understanding of how diabetes affects the development of ALI/ARDS is important for prevention and management of ALI and will indicate the future public health impact of ALI/ARDS. Although the ARDS Network has accomplished much in determining the optimal treatment strategy for patients with ALI/ARDS, relatively little attention has

been directed toward preventing this devastating condition. A better understanding of the predictors for development of ALI/ARDS will be important in risk-stratifying individual patients and determining who will require more intensive care and monitoring. Such knowledge will allow investigators to identify high-risk patients for clinical trials aimed at prevention.

Because ALI is one of the most common conditions encountered in the ICU and carries a high burden of morbidity, health care cost, and mortality, it is important that we understand the role of insulin in ALI/ARDS so we can determine the appropriate patient population and the optimal clinical conditions for insulin therapy in the critically ill patient. An understanding of how insulin modulates inflammation and lung injury may clarify whether the glycemic or the nonglycemic effects of insulin are important in critical illness. Such understanding is crucial in the debate on the optimal glucose targets in insulin therapy in the ICU. Other medications for diabetes, such as PPAR- γ agonists, metformin, ACE inhibitors, and statins, may open the gate for development of novel pharmaceuticals to prevent ALI/ARDS.

A multidisciplinary, multifaceted approach is needed. Animal studies of type 2 diabetes that use different injury models after treatment with insulin or other diabetic therapies are needed to clarify the mechanisms by which diabetes may protect against the development of ALI/ARDS. Carefully designed clinical studies with rigorous phenotyping of diabetes, diabetic management, and ALI are vital to determine the clinical conditions by which diabetes may be beneficial or detrimental in ALI and to determine whether insulin, PPAR- γ agonists, ACE inhibitors, statins, and other therapies used in diabetes either explain or modify the effect of diabetes on ALI. Given the recent evidence for genetic susceptibility to ALI/ARDS, it will be interesting to search for potential gene-gene interactions between genes important in diabetes and metabolism and genes implicated in inflammation and ALI/ARDS. How individual genetic heterogeneity influences response to therapies like insulin or ACE inhibitors also should be investigated.

When the outcome of interest is the development of ALI, careful attention to timing is crucial. In all of the studies discussed here, therapies like insulin or rosiglitazone were given early, either just before or just after the injury and before development of lung injury. Given that ALI typically develops rapidly with a median of 1 day (25% to 75%, 0-3 days) after ICU admission (16), any potential intervention aimed to prevent lung injury must be implemented as early as possible, preferably before ICU admission. The concept of a crucial window of opportunity is not new in the field of critical care medicine. Goal-directed hemodynamic therapy in sepsis was recently found to be beneficial only after early implementation before ICU admission (121). Recently, studies have suggested that the timing of hyperglycemia and insulin treatment in critical illness is important. Hyperglycemia early in trauma predicts worse outcomes than hyperglycemia in later stages of the ICU stay (122). Initiation of intensive insulin therapy in critically ill hyperglycemic patients within 48 hrs of ICU admission was associated with better outcomes compared with delayed initiation of insulin (123).

CONCLUSION

ALI/ARDS is a devastating illness with high morbidity and mortality rates. Research has shown an association between diabetes and decreased risk of lung injury, but our understanding of how diabetes may affect the development of lung injury is limited. Recent studies suggest that hyperglycemia and the nonglycemic sequelae of diabetes may play a role. The common therapies used in diabetes, like insulin and PPAR agonists, may also influence the development of ALI and modify or counteract the effect of diabetes on ALI/

ARDS. Given the increasing incidence of diabetes and sepsis, the latter of which is the leading cause of ALI/ARDS, defining the role of diabetes and its treatment in the development of lung injury is important to determine the direction of ALI/ARDS research. Multidisciplinary, multifaceted studies, both at the bench and at the bedside, are essential.

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Figure 1. Adjusted odds ratio for development of acute lung injury/acute respiratory distress syndrome with diabetes (14,16,17).

Figure 2. Complex relationship between diabetes and acute lung injury (*ALI*)/acute respiratory distress syndrome (*ARDS*). Intersection of hyperglycemia, metabolic abnormalities, inflammation and therapeutic agents.

Figure 3.
 Mediators found in the pathogenesis of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) and its interactions with insulin.

Table 1
Characteristics of observational studies exploring the association between diabetes and ALI

Risk Factor for ALI/ARDS	Study Design	Study Size	Number of Patients with Diabetes	Admission Glucose (mg/dL) among Patients who Developed ALI/ARDS	Admission Glucose (mg/dL) among Patients who Did Not Develop ALI/ARDS
Iscimen et al (17)	Septic shock Medical intensive care unit in a tertiary hospital	160	55	Not available	Not available
Gong et al (16)	Sepsis, septic shock, pneumonia, trauma, multiple transfusions or aspiration	688	164	182 [95% CI :144-249]	178 [95% CI :142-237]
Moss et al (14)	Septic shock 4 centers	113	32 66% on insulin; 34% on oral agents	110 [95% CI :87-180]	152 [95% CI :109-234]

ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

Commonly prescribed therapies for diabetics and their mechanisms of action

Table 2

	Reduce Pro-inflammatory Cytokines	Reduce Oxidative Injury	Reverse State of Dyslipidemia	Reduce Neutrophil Chemotaxis and Leukocyte Adhesion	Modulate Inflammation (noncytokine mediated. e.g. MBL, NF-kB)	Regulate Apoptosis	Ameliorate Pro-Coagulant State	Regulate Cellular Proliferation	Prevent Endothelial Dysfunction	Attenuate Catabolic State of Critical Illness
Insulin	✓	✓	✓	✓	✓	✓	✓	???	✓	✓
ACE-I	✓	✓	±	✓	✓	✓	✓	✓	✓	
PPAR agonists	✓	✓	✓	✓	✓	✓	✓	✓	✓	
HMG CoA reductase inhibitors	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Metformin	✓	✓	✓	✓	✓		✓		✓	

NF-KB, nuclear factor-kB; ACE, angiotensin-converting enzyme; PPAR; peroxisome proliferator-activated receptor.

^aIn non-critically ill patients, insulin has been shown to be a mitogen with anabolic properties. Contrary to expectation, however, in critically ill patients, serum insulin-like growth factor-1, acid-labile subunit, insulin-like growth factor binding protein -3, and GH binding protein levels are further suppressed rather than increased with intensive insulin therapy, mimicking a state of relative growth hormone resistance.