Research Article

Pulmonary Infectious Diseases in Association with Diabetes Mellitus

Abstract

Type II diabetes mellitus affects all age group and may underestimated in clinical practice. Approximately, 38 % of adults admitted acutely to the general hospital wards are identified to have hyperglycemia. Various associated adverse outcomes in hyperglycemic patients include severe hospital-acquired pneumonia, severe pulmonary infections with antimicrobial resistance, particularly *Staphylococcus aureus* and *Pseudomonas aeruginosa*, acute myocardial infarction, trauma, diabetic nephropathy, and diabetic retinopathy. Airway-surface-liquid glucose concentration play a major role in protecting the lungs against microbial infections. Currently, there is limitation regarding the knowledge about the interaction of human respiratory cell defense with respiratory pathogens in diabetic patients.

Keywords: Diabetes mellitus; airway surface liquid: pulmonary infection; glucose concentration

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Abbreviations: ADA, american diabetes association; ASL, airway surface liquid; ATPase, adenosine triphosphatase; CI confidential interval; COPD chronic obstructive pulmonary disease; DM diabetes mellitus; EBC exhaled breath condensate; GLUT, glucose transporter; ICU, intensive care unit; mRNA, messenger Ribonucleic Acid; MRSA, Methicillin-Resistant *Staphylococcus aureus*, SD, standard deviation; WHO, world health organization

Introduction

Currently, the diagnosis of diabetes mellitus (DM) depends on either a fasting plasma glucose that is at least 7 mmol/liter, or the clinical manifestations of DM plus a causal plasma glucose is at least 11.1 mmol/liter. Impaired fasting glucose is a fasting plasma glucose at least 6.1 mmol/ liter, and impaired glucose tolerance is a plasma glucose of 7.8-11 mmol/liter, 2 hours after an oral glucose load. The risk of DM developing in later life is increased by fasting plasma glucose greater than 6.1mmol/liter. These definitions are defined by the World Health Organization (WHO) and the American Diabetes Association (ADA). The plasma glucose threshold for developing diabetic retinopathy is estimated to be as low as 7 mmol/ liter, whereas coronary heart disease is commonly developed with fasting plasma glucose greater than 5.8mmol/liter.[1–3] Increasing type II DM, compounded by the increased prevalence of sedentary habit and obesity contributes to increasing prevalence of DM.[4] Type II DM affects all age groups and may greater underestimated in clinical practice.[4] Chronic hyperglycemia in DM due to relatively or absolute insulin deficiency results in characteristic clinical manifestations and is strongly associated with the severity of neurologic and micro vascular complications.[5] Normal clearance mechanism may interfere and disturb pulmonary immune cell function.[6] It is postulated that hyperglycemia affects the lungs by the non-enzymatic glycosylation of collagen and by damaging capillaries.[7] Umpierrez et al. demonstrated that 38% of adults admitted acutely to the general hospital wards were identified to have hyperglycemia.[4]

Approximately, one-third of the patient group with hyperglycemia had been newly diagnosed, and in-hospital mortality was higher in this group than in those with diagnosed DM or normoglycemia (16% versus 3% versus 1.7%, respectively).[4] Furthermore, those patients with newly-diagnosed hyperglycemia frequently had longer hospital stay and intensive care unit (ICU) admission.[4] Various associated adverse outcomes in patients with hyperglycemia was revealed, such as ischemic or hemorrhagic stroke,[8] acute myocardial infarction,[9] trauma,[10] and surgery.[11] An increase in blood glucose concentration of 1 mmol/liter is associated with a 3% increase in the risk of in-hospital complications.[12] Approximately, 50% of patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) have a blood glucose concentration of equal to or above 7.0 mmol/ liter and *Staphylococcus aureus*, particularly Methicillin-resistant *Staphylococcus aureus* (MRSA) (relative risk 2.1 (95% Confidential Interval (CI) 1.2, 3.8)) is more frequently isolated from sputum.[13] Glucose containing in the airway secretions of intubated patients is associated with ICU acquisition of respiratory infections.[14]

In ICU-admitted patients, glucose in airway secretions are associated with subsequent MRSA acquisition of MRSA (relative risk 1.8 (95 % CI 1.1, 3.6)), indicating that glucose precedes infection. Bacterial organisms utilize saccharides both as substrates for catabolic reactions to provide energy for growth and as carbon for the biosynthesis of new cellular material.[15] The relative risk of death or prolonged hospital stay increases by 14 % with each 1 mmol/ liter increase in blood glucose concentration.[13] In ICU-admitted patients with stress hyperglycemia, the nasal-secretion glucose concentrations are 1-11 mmol/liter, whereas the nasal secretion concentrations are 1-9 mmol/liter in patients with treated DM.[16] Both *Staphylococcus aureus* and *Pseudomonas aeruginosa* possess transporters that allow cellular uptake of D-glucose and are able to metabolize D-glucose.[17,18] *In vitro*, airway-secretion glucose concentrations of 0.5-10mmol/liter and 0.56mmol/liter promote a dose-dependent increase in the growth of

Staphylococcus aureus and *Pseudomonas aeruginosa*, respectively.[19] A previous *in vitro* study demonstrated that glucose concentration of approximately 50mmol/liter can induce algD transcription and increase the production of alginate, a viscous exopolysaccharide that causes lung deterioration in cystic fibrosis.[20] Pathophysiological glucose concentrations can stimulate both *Staphylococcus aureus* and *Pseudomonas aeruginosa* (11.1mmol/liter) to form biofilms, adherent slime-encased bacterial communities that allow bacterial survival and antimicrobial resistance.[21] Elevation of serum concentrations of proinflammatory cytokines, including interleukin-6,[22–24] soluble interleukin-6 receptors,[22–24] interleukin-8,[25] and tumor necrosis factor-alpha[22,24] can be identified in patients with impaired glucose tolerance, compared with individuals with normal glucose tolerance.

Glucose concentration in airway surface liquid

Some previous animal studies demonstrated that the glucose concentration of airway surface liquid (ASL) is 3-20-fold lower than that of plasma.[26] In healthy human volunteers, glucose has not been detected in their nasal secretions,[16] but contain 0.4 (SD 0.2) mmol/liter in exhaled breath condensate (EBC) collection.[27] In diabetic patients, glucose in EBC contains 1.2 (SD 0.7) mmol/liter, compared with 0.4 (SD 0.2) mmol/liter in ASL from normal subjects (p < 0.0001).[28] In normoglycemic healthy subjects with acute viral rhinitis, nasal-secretion glucose is detected at 1-2 mm and disappears with clinical resolution.[16] In patients with pulmonary cystic fibrosis who have normal glucose tolerance and airway inflammation, the ASL glucose concentrations are elevated.[29] In normal individuals, glucose concentrations are 10-fold lower in airways than in plasma indicates that glucose is actively removed from the airway lumen against the glucose concentration gradient. Several previous animal studies have demonstrated that glucose is removed from the airway lumen by Na^+-dependent glucose transporters in the apical membrane of the airway epithelial cells[26,30] and is driven by a Na^+ gradient that is generated by Na^+-K^+ ATPase pumps in the basolateralmembrane of epithelial cells.[31] Animal airway epithelial cells also express the facilitative GLUT.[31] Na^+-dependent glucose transporter-1 and GLUT2 are expressed at mRNA and protein level immortalized cell lines from the proximal (H441) and distal (A549) airway,[32] indicating that glucose homeostasis is similar in human airways. Airway inflammation could elevate airway glucose concentrations by increase glucose movement into the airway lumen and reduce the Na^+ gradient driving glucose transport out of the lumen. Nevertheless, how the lung epithelium maintains correct glucose homeostasis in the face of a hyperglycemic challenge, particularly when associated with chronic pulmonary diseases, is poorly understood. A recent research project has been carried out by Baines et al.[33] at St George' s, University of London, United Kingdom to develop molecular sensors for the measurement of glucose in airway secretions.[33]

Discussion

Hyperglycemia induces increases in ASL glucose concentration are associated with increased airway bacterial load by using *Pseudomonas aeruginosa* with targeted gene deletions in the glucose metabolism pathway in several previous studies. One example of a number of non-immune mechanisms that have evolved to prevent bacterial infection is controlling airway glucose concentration. Levels of amino acids and other carbon sources in the airways are restricted as well as glucose.[34] Competition and interactions between bacterial organisms for this restricted resource can contribute to alteration of bacterial virulence.[35] Glucose is important in host immune function. Bacterial exposure can increase cellular glucose uptake.[36] The competition between human lung cells and bacteria for airway nutrients is of interesting need for further research, particularly the actions of anti-diabetic drugs on the human-lung immune cells. ASL chemistry has an effect on the secretion and action of antibacterial molecules, in addition to directly affecting bacterial growth and survival. Airway surface pH has been shown to be significant for function of pulmonary antibacterial activity.[37] Glucose can inhibit the secretion of anti-microbial peptides in the airways induced by bitter taste receptors.[38] Glucose can also inhibit the function of surfactant protein D.[39] The predisposition may be based on conditions that interfere with normal clearance mechanisms or disturbance of pulmonary immune cell function and could be further to be complicated by coexisting medical conditions, such as cardiovascular disease, vascular insufficiency, chronic renal disease, and malnutrition. Current knowledge about the interaction of the human host cell defense with respiratory pathogens is limited due to incomplete knowledge regarding specific pulmonary immune mechanisms in diabetic individuals.

Conclusion

Maintaining the low ASL glucose concentration in human airways is critical for protecting the lungs against infection. Changes in pulmonary epithelial permeability and epithelial glucose metabolism or transport could be resulted from elevation of ASL glucose concentrations in patients with pulmonary inflammation.

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Conflcit of interest

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