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IS LUNG A TARGET OF DIABETIC INJURY? THE NOVEL PRO AND CONS EVIDENCES

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The rationale for questioning whether lung is/ or is not affected by diabetes is based on two reasons: the frequent dysfunction of the lung encountered at the newborn children of diabetic mothers and the need to understand the pathophysiology of this organ for anti-diabetics administration by inhalation. This review attempts to give an answer to the above dilemma, based on the most recent results. With this aim, Medline and PubMed data bases have been searched for the interval 2009-2013 (terms: lung, diabetes mellitus). The search showed that diabetic lung is the site of microangiopathic changes; the functional parameters decline, the oxidative and inflammatory stress is installed, while the antioxidant defense is diminished. The consequence of diabetes-induced lung modifications is the increased risk for obstructive, inflammatory, and infectious diseases. In obesity, "the fatty diabetic lung" is subjected to the additional harmful effects of lipotoxicity. Meanwhile, few authors claim that the vascular and ventilation reserves may compensate for diabetes-induced lung dysfunction. Examination of balance between the Pro and Cons evidences shows that it tilts towards the Pro side, as justified by the prominent modifications occurring in diabetic lung, which eventually conduct to alterations in gas exchange.

Key words: microangiopathy, obesity, hypertension, insulin, pulmonary surfactant.

INTRODUCTION

Whether diabetes mellitus affects/or not the lung is a long lasting dilemma that deserves nowadays a clear-cut answer. The urgency is provided by the need to understand fetal lung inheritance of maternal diabetes traits, and by the current exploitation of lung large surface area and good vascularization for systemic delivery of anti-diabetic drugs. The recent reports demonstrate delayed alveolization and reduced amounts of protein D associated to surfactant (PS) in the lungs of newborn children of diabetic mothers; the associated respiratory distress syndrome installed explains the increased morbidity and mortality of those children[1]. Moreover, several biochemical changes induced by maternal diabetes in fetal lung have been recently uncovered, such as the reduced PPARα concentration, the increased iNOS expression, and the NO overproduction[2]. For the oral inhalation of anti-diabetics, it is essential to be aware of potential diabetes-associated pulmonary dysfunction (that may amend the absorption and bioavailability of inhaled drugs) and of drugs safety in a chronic administration. Small size insulin particles (with a mass median diameter of less than 2 microns, able to attain the alveoli), Technosphere insulin (TI), or large recombinant human insulin (rh-insulin) have been recently employed as inhalants; the strategy to facilitate the absorbtion of the latter consists in use of absorbtion enhancers such as the natural PS or its artificial substitute, phospholipid hexadecanol tyloxapol (PHT)[3-5].

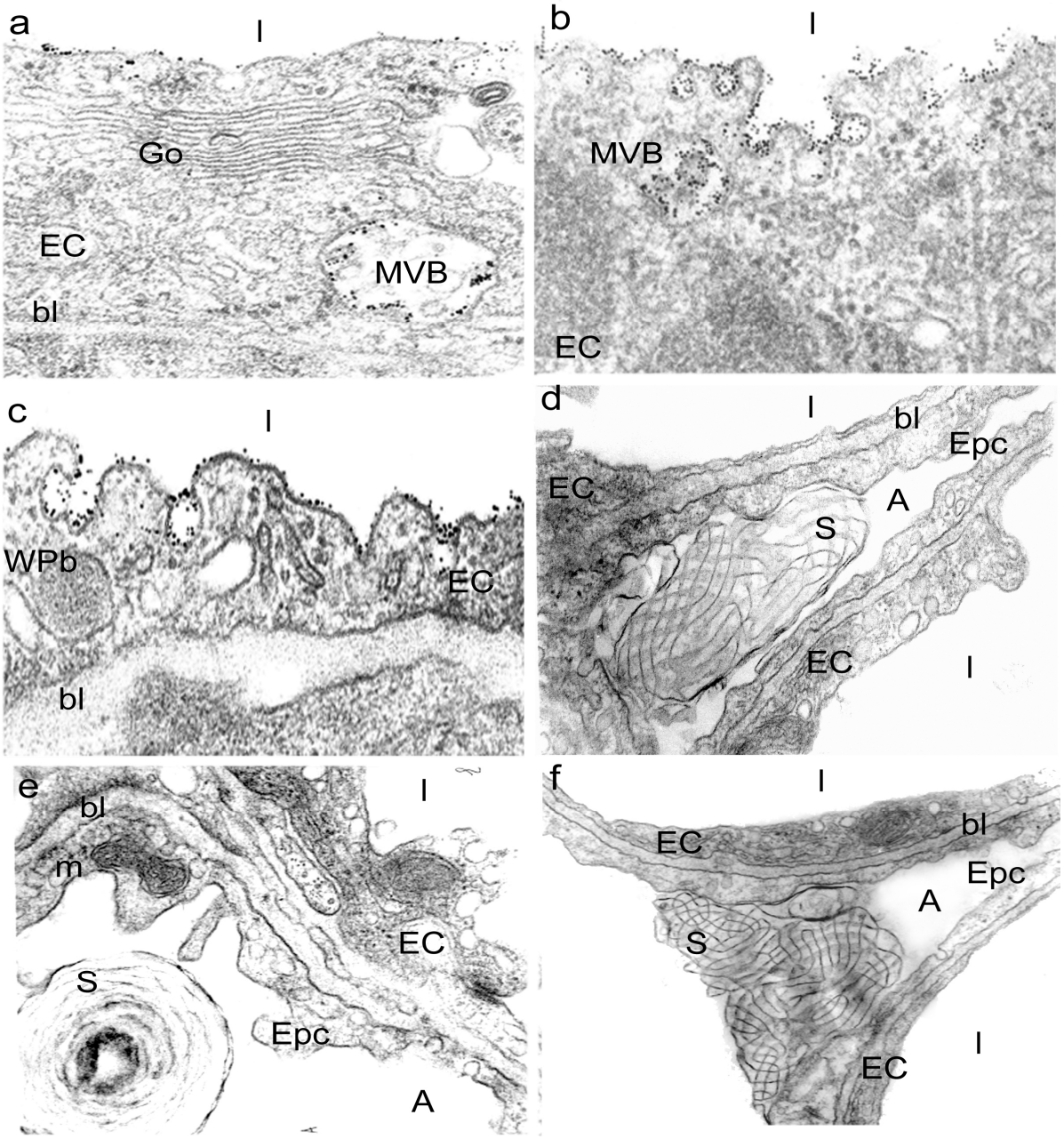

Fig. 1. Electron microscopic images of the lung in experimental Type 1 diabetes mellitus: (a) the metabolically active phenotype of capillary endothelium (EC),(b) Albumin-AGE.Au uptake and transport by EC, (c) the enlarged EC basal lamina (bl), (d,f) the surfactant (S) squeezed within a narrow alveolar space (A), (e) the surfactant cluster before covering the alveolar epithelial cells (Epc). The black dots: the electron opaque 5nm gold particles in Albumin-AGE.Au perfused conjugate; l: capillary lumen; Go: Golgi complex; WPb: Weibel Palade body; MVB: multivesicular body; m: mitochondria. Magnification: 1cm=0.14µm (a,b), 0.16µm (c),0.20µm(d,e), 0.54µm(f.)

As for the safety, it was shown that inhaled insulin rapidly forms amyloid within the lungs causing a significant reduction in pulmonary air flow (*i.e.* decreasing the pulmonary capacity)[6]. Besides insulin, novel anti-diabetic inhalant preparations have been synthesized, aiming either augmented resistance to proteolysis (such as PEGylated glucagon-like peptide-1(7-36) GLP-1)[7] or a long time effect (the nanogels made of deoxycholic acid-modified glycol chitosan,

DOCA-GC containing palmityl acylated exendin-4, Ex4-C16)[8]. From these examples, one can safely conclude that the search for new inhalant anti-diabetic preparations is ongoing.

The purpose of this review is to critically evaluate the new results on the impact of diabetes on lung structure, function, and biochemistry, and to emphasize the emergent pathological implications. With this aim, we searched the Medline and PubMed data bases for the interval 2009–2013 (terms: lung, diabetes mellitus). Taking into account the overwhelming evidences, the lung emerges as a target organ for diabetic microangiopathy; when an associated acute or chronic pulmonary and/or cardiac disease coexists, severe respiratory derangements in diabetic patients may occur.

Evidences for lung as a target of diabetic injury: microangiopathy and impaired function

As for other capillary beds altered by diabetic hyperglycemia in terms of structure and function, the lung extensive microvascular circulation and abundant connective tissue are potential candidates for such modifications. Indeed, in a model of Type 1 diabetes mellitus (mice and hamsters injected with streptozotocin) we noticed lung cells structural and functional modifications[9,10]. Electron microscopic examination shows that capillary endothelial cells turn to a metabolically active phenotype, with well-developed biosynthetic and degradation organelles (*versus* the quiescent phenotype, in physiological condition) (Fig. 1, a), their basal lamina becomes thickened (Fig. 1, c), and the extracellular matrix develops hyperplasia. Under the pressure exerted by the latter, narrowing of ~30 % of capillaries occurs. It is obvious that the narrowed capillaries will contribute to the decline in capillary blood volume, a feature acknowledged also in the model of Zucker diabetic fatty rats[11,12]. In terms of function, the capillary endothelial cells display numerous caveolae (often fused) that transport intensely the blood components from the lumen to the tissue, and suggest the augmented permeability of the pulmonary microvasculature (Fig. 1b and c). Other changes are recorded the alveolar side of the blood-air barrier. The volume of lamellar bodies was higher *vs.* the lung of nondiabetic, lean animals[11]. These organelles package and excrete surfactant (a surface-active phospholipoprotein complex) (Fig. 1 e), that subsequently covers the alveolar epithelium as a monolayer, and reduces surface tension. Moreover, the alveolar epithelium appears as collapsed, compressing surfactant within the air space (Fig. 1d and f). To this feature may contribute the increase in alveolar septum thickness, as reported recently[13]. Taken together, the above changes prove for diabetes-associated microangiopathy of pulmonary capillaries, a process accompanied by autonomic neuropathy, myopathy of respiratory muscles, or by collagen changes[14]. For better understanding lung microangiopathy, its diagnosis and monitoring at diabetic patients it is recommended application of perfusion chest computed tomography[15].

Interestingly, progression of systemic microangiopathy can be estimated by measurements of the lung functional parameters[16]. The novel data sustain several abnormalities of the respiratory function encountered in patients with type 1 and type 2 diabetes mellitus. These abnormalities consist in reduced forced expiratory volume in first second (FEV1)[14,17-20], lower forced vital capacity (FVC)[14,17-22], decreased diffuse lung capacity for carbon monoxide (DLCO)[14,20,22], lower basal bronchial tone, lower cough reflex sensitivity, and disorders in respiratory muscles or phrenical nerve[14,23]. These parameters assess the decline in respiratory function at both type 1 and type 2 diabetic patients. Moreover, the impaired lung function is negatively correlated with glycemic status and duration of diabetes, and suggests the setting of a fibrotic process[24,25]. The new data show that Ang II plays a critical role in diabetic lung fibrosis, which is most likely caused by NOX activation-mediated nitrosative damage[26].

Furthermore, diabetic patients are at increased risk of several pulmonary complications such as chronic obstructive pulmonary disease (COPD), asthma, inflammatory, and infectious diseases[24]. Diabetes causes pulmonary infiltration/recruitment of macrophages and other inflammatory cells[27-29] and the inflammatory process seems to be beyond association between COPD and type 2 diabetes[30]. Other respiratory abnormalities in diabetic patients are caused by infections[14,31,32]. Reportedly, the decline in autoimmunity leading to increased susceptibility to infections may be due to impaired

alveolar macrophages function[33]. There is a suggestion that the low glucose concentration in airway surface liquid may contribute to lung defense against infections[34]. Taken together, the above modifications recorded in diabetic lungs eventually conduct to alterations in gas exchange.

Diabetes and obesity disturb lung biochemistry

As for other organs/tissues exposed to diabetic hyperglycemia, installment of oxidative stress is the most acknowledged change in lung biochemistry; meanwhile the lung antioxidant capacity is decreased[13,35]. Other biochemical modifications consist in increased levels of inflammatory mediators[17] and in the lower expression of CCAAT enhancer-binding proteins, such as C/EBPβ and C/EBPδ[36]. The attempts to reverse the disturbed biochemistry include: use of antioxidants such as vitamin E, the N-acetylcysteine, and aminoguanidine[13,35,37] and the diminishment in SOD within extracellular matrix[27]. In obesity, dysfunction of the "fatty diabetic lung" is exacerbated, along with diffusion impairments[12,38]. Moreover, by hampering lung expansion, visceral obesity causes a restrictive ventilation pattern[39]. As for structural modifications, the "fatty diabetic lung" shows extensive lipid deposition within alveolar interstitium, lipofibroblasts, and macrophages, altered ultrastructure of type 2 epithelial cells, and surfactant protein expression patterns that suggest additive effects of hyperglycemia and lipotoxicity[11]. It is also important to note that diabetes might be a risk factor for pulmonary hypertension[29], while sepsis conducts to a lower risk of respiratory dysfunction[40].

The Cons arguments

Opposite to the evidences of lung structural, functional and biochemical changes induced by diabetes mellitus and obesity, several authors argue with the lack of reports on limitations of daily activities ascribable to pulmonary disease in diabetic patients[41], and with the existence of significant vascular and ventilation reserves that may compensate for diabetes-induced dysfunction[42,43]. Other authors have a rather moderate answer, recognizing that diabetes is associated with a modest, albeit statistically significant diminished pulmonary function[44].

CONCLUSIONS

The balance between Pro and Cons novel evidences supports the conclusion that lung is a target organ for diabetic microangiopathy; moreover, the presence of an associated acute or chronic pulmonary and/or cardiac disease could aggravate the diabetes-associated respiratory dysfunction. At the horizon, two new lines of investigation emerge: "diabetic lung" as model of accelerated aging[23], and the study on lung transplant adult recipients which are prone for development of new-onset diabetes mellitus[45].

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