EDITORIAL
COPD

Skin autofluorescence: early sign of lung function deterioration?

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The relationship between SAF and FEV_1, D_{LCO} and X_5, independent of COPD or diabetes. Will individuals with raised SAF and subclinical lung function alterations develop disease? What mechanisms underlie parenchymal alterations indicated by SAF? https://bit.ly/2YTtdkL

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Advanced glycation end products (AGEs) comprise a heterogeneous group of stable end-products of the non-enzymatic glycation reactions described by Maillard in 1912, in which reduced sugars irreparably modify proteins, lipids and DNA. This is a slow physiological process and accumulation of AGEs is part of normal ageing. Under conditions of hyperglycaemia and oxidative stress, a much faster and more substantial generation of AGEs is induced. The myriad of pathogenic signals AGEs can induce and the fact that enhanced AGE accumulation accompanies a broad spectrum of age-associated chronic inflammatory diseases [1] form the basis of the Maillard theory of ageing [2].

A number of AGEs are characterised by their yellow-brown fluorescent colour and their ability to form stable molecular crosslinks on long-lived proteins such as skin collagens [3, 4]. The skin offers an excellent opportunity for noninvasive investigation of AGE accumulation, through their auto-fluorescent properties [5]. As such, glycation-associated skin autofluorescence (SAF) correlates with chronological ageing in healthy subjects [6] and enhanced accumulation of AGEs in the skin has been detected in diabetes [4, 6]. In the search for (noninvasive) biomarkers for COPD, studies have shown increased SAF in COPD as well, which inversely correlated with indices of lung function. In the current issue of *ERJ Open Research*, the study by Zaigham *et al.* [7] is only the second to extend these findings into a population-based study, of mostly 50–64-year-olds.

Here, Zaigham *et al.* [7] examined the relationship between SAF and detailed lung function measures using impulse oscillometry (IOS) and diffusing capacity in the population-based cohort SCAPIS (Swedish CArdioPulmonary bioImage Study). Subjects with SAF in the highest tertile were generally older, more likely to be current smokers, and represented a larger proportion of patients with COPD and diabetes, reflected by higher mean values of HbA1c, and lower mean values of spirometry and diffusing capacity. When correcting for confounders, or restricting the analyses to nonsmokers or subjects without COPD, inverse relationships between SAF and forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (D_{LCO}) and DLCO/alveolar volume remained significant. From the IOS data, it appeared that SAF was especially related to respiratory reactance, namely as an inverse correlation with reactance measured at 5Hz. This relationship was again also apparent in non-COPD subjects, but absent in nonsmokers. The association with FEV_1 has been shown in previous studies in patients with COPD [8–10], whereas the loss of a significant relationship between SAF and the

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FEV_1/FVC ratio after correcting for multiple confounders is in contrast to previous reports in healthy patients and COPD patients [10, 11].

Based on the observed association of SAF with D_{LCO}, the authors speculate about relationships to changes in the lung parenchyma, either emphysematous or fibrotic in nature. The diffusing capacity is determined by two components, the alveolar–capillary membrane diffusing capacity and the pulmonary capillary blood volume [12]. Previous studies in diabetes indicated that a reduction in alveolar–capillary membrane diffusing capacity can be related to thickening of the pulmonary capillary basal lamina or increases in endothelial permeability, resulting in an overall reduction in D_{LCO} [13–15]. Pulmonary capillary blood volume is determined by the number of pulmonary capillaries in contact with ventilated alveoli, which is also reduced in conditions such as diabetes [16]. This subclinical attenuation of lung function, reflected in a restrictive spirometric pattern and impaired diffusing capacity, is well recognised in diabetics [13, 14]. Moreover, already at a pre-diabetes stage, negative effects on lung function have been reported [17, 18]. The impaired lung function in diabetes is associated with glycaemic control and disease duration, both of which are associated with increased AGE levels [18–20]. The non-enzymatic glycation of pulmonary extracellular matrix components is often proposed as the mechanism underlying the negative effects of hyperglycaemia on lung function, but this has never been examined. Moreover, although enhanced SAF in diabetics has been associated with (micro)-vascular complications [21], it has not been examined in relation to lung function. It seems plausible to link the accumulation of AGEs to these intermediary processes rather than to specific parenchymal abnormalities (destructive or fibrotic).

The authors hypothesise that the reported inverse association between SAF and X_5 could be linked to changes in elastance of the respiratory system. However, data obtained by oscillometry and pulmonary mechanical resonance imaging clearly indicate that increased ventilation heterogeneity in never-smokers and ex-smokers without COPD did not reflect in qualitatively apparent changes in oscillometry. Therefore, this isolated relationship between X_5 and SAF must be cautiously interpreted in terms of underlying airway and parenchymal biomechanical abnormalities [22]. A relationship with emphysema is assumed based on its strong associations with the receptor for AGEs (RAGE). However, it is of interest to note that AGEs elicit more broad pathogenic effects than solely through activation of RAGE. AGEs can indeed directly impact the stiffness of the extracellular matrix, as well as disturb matrix turnover in favour of collagen deposition [23].

It remains unclear to what extent SAF serves as a proxy for AGEs in general. AGEs are formed through various sequential chemical reactions and consist of a broad range of compounds. Because not all AGEs have auto-fluorescent properties, their measurement through autofluorescence only represents a portion of them.

It is poorly understood if and how SAF relates to AGE accumulation and effects thereof in other organs, including in disease. To minimise external influences, such as from UV light, it is recommended to measure SAF on the volar side of the arm. Cigarette smoke accelerates skin ageing and contains glycotoxins that induce AGE formation [24]. Enhanced SAF has indeed been shown in smokers compared to nonsmokers [25, 26], as did the study by Zaigham *et al.* [7]. Some studies particularly measured SAF in the non-dominant arm to limit external effects of smoking. Direct effects of smoke are therefore less likely to underlie SAF, but cannot be ruled out.

AGEs transported through the circulation are the most attractive connection between SAF and other organs. Elevated circulating AGE levels are a result of imbalanced uptake through the diet, intake *via* smoking and endogenous production *versus* elimination. In various chronic inflammatory conditions enhanced circulating AGE levels were measured, but very few studies investigated associations between SAF and circulating AGEs. When we examined the association between three different plasma AGEs and SAF, surprisingly only significant relationships with the non-fluorescent AGEs N(6)-carboxymethyllysine (CML) and Nε-(carboxyethyl)lysine (CEL) were observed. For plasma CML, which decreased in COPD patients, this was even an inverse association. One study reported on the differential accumulation in skin, plasma and lung tissue in COPD patients. Hoonhorst *et al.* [9] found increased SAF, but no evidence of enhanced levels of AGEs in plasma, sputum or bronchial biopsies. This is in contrast to earlier reports of increased plasma CEL levels and accumulation of AGEs in lungs of COPD patients, which both negatively correlated with lung function [27, 28]. Also in the lining fluid of COPD patients, CML was increased compared to healthy ex- and current smokers [28].

These discrepancies can likely be attributed to the various methods employed to measure AGEs. Mass spectrometry is the most sensitive, specific and reliable method to measure AGEs. Commercially available antibody-based assays are more commonly used, but lack specificity. Finally, fluorescence-based assays only capture a fraction of AGEs.

In general, the interpretation of AGE measures or proxy's thereof across different organs is complicated by the complex chemistry behind AGE formation, the multiple sites of origin, the variable turnover rate of targeted proteins and equilibrium between formation and elimination.

Regardless, enhanced levels of circulating AGEs represent a potential common underlying mechanism of multi-organ and multi-morbid conditions that are often observed in the elderly, in which vascular effects are a common denominator. Diabetes and its complications form the basis for this theory. Moreover, data support the role for AGEs in the onset and progression of cardiovascular diseases through different mechanisms including direct effects on vascular stiffness, pro-inflammatory effects, endothelial dysfunction and pro-coagulant activity [29, 30]. Interestingly, in COPD enhanced AGE presence has been seen in endothelial cells of both the lungs and the kidneys, which was linked to endothelial damage [31]. Within this theory, there might be an opportunity to use SAF as an early biomarker, as it has been associated with the individual conditions, but follow-up examinations are needed to look into specific organs affected.

With respect to the lungs and their functioning, IOS is a sensitive method and is able to detect more subtle changes when compared to standard spirometry. As such, it could be more useful to establish an earlier diagnosis or monitor more subtle changes over time. As stated by the authors, it would be of great interest to examine whether individuals with raised SAF and subclinical lung function alterations determined by IOS and/or diffusing capacity will go on to develop disease. Furthermore, it would be important to confirm these IOS abnormalities and their possible association with SAF in other cohorts.

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