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Subcutaneous advanced glycation end-products and lung function according to glucose abnormalities: The ILERVAS Project

The lung is not usually included in the list of organs that might be affected by type 2 diabetes (T2D). However, its abundance of collagen and elastin fibers, crucial proteins in the extracellular matrix, together with its vascularization reach, make the lung parenchyma a potential target for chronic hyperglycaemia [1]. Indeed, cross-sectional studies conducted during the past few decades have shown that adults with T2D have lower forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1) than adults without T2D [2]. A few pathophysiological mechanisms have also been well documented, including insulin and leptin resistance, low-grade chronic inflammatory status, microvascular lung damage and autonomic neuropathy [1].

However, little is known of the potential relationship between advanced glycation end-products (AGEs) and lung function, and what scarce information there is has been focused on patients with chronic obstructive pulmonary disease (COPD), in which higher skin AGE deposition and plasma AGE concentrations have been reported [3]. Yet, the relationship between AGEs and pulmonary function, taking into account the presence of glucose abnormalities, has not been previously examined. For this reason, skin AGE accumulation and spirometric maneuvers were assessed in a large population with no known pulmonary disease according to the presence of glucose abnormalities.

Both our control and prediabetes populations were recruited from a total of 1924 Caucasian subjects enrolled between July 2015 and May 2017 into the ILERVAS project (ClinTrials.gov Identifier: NCT03228459). This ongoing randomized interventional study is concerned with early diagnosis of subclinical vascular and "hidden" kidney diseases [4]. Inclusion criteria were: age between 45–70 years; no history of cardiovascular disease or T2D; and at least one cardiovascular risk factor (obesity, hypertension, dyslipidaemia, smoking or first-degree relative with premature cardiovascular disease). Exclusion criteria were: COPD; T2D; chronic kidney disease; active neoplasia; life expectancy < 18 months; pregnancy; and darker skin color (Fitzpatrick scale types > 5).

Smokers who had stopped smoking ≥ 1 year prior to recruitment were considered former smokers. Prediabetes was diagnosed in 34.6% ($n = 660$) of subjects according to American Diabetes Association criteria [glycosylated haemoglobin (HbA_{1c}): 39–47 mmol/mol or 5.7–6.4%]. Also, 79 age-matched T2D patients were recruited from the outpatients diabetic clinic of University Hospital Arnau de Vilanova in July 2017. Informed consent was obtained from all participants, and the protocol was approved by the Arnau de Vilanova University Hospital ethics committee.

Anthropometric data were obtained by standardized protocols. Glycosylated haemoglobin was determined using the cobas b 101®

system (Roche Diagnostics International, Rotkreuz, Switzerland). Dry samples of capillary blood were used for analyses of values of total cholesterol and serum creatinine.

Forced spirometry was performed using a portable ultrasonic spirometer (Sibelmed Datospir, Sibel S.A., Barcelona, Spain). Subjects were required to have at least three reproducible measurements, and the output with the highest total FEV1 and FVC scores was used for analyses. Various spirometric parameters were measured as a percentage of predicted values. "Normal" FEV1 was defined as a value $\geq$ 80% of that predicted, a "non-obstructive ventilatory defect" as an FVC < 80% of predicted value with an FEV1/FVC ratio $\geq$ 70%, and an "obstructive ventilatory defect" as an FEV1/FVC ratio < 70%, as per criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).

Skin autofluorescence (AF) was measured on the left forearm using the AGE Reader™ (DiagnOptics, Groningen, Netherlands), a fully automated, non-invasive, non-operator-dependent desktop device that uses ultraviolet A (UVA) spectrum wavelengths. The mean AF value of three readings, expressed in arbitrary units (AU), was recorded. The same device was used for measurements in all participants.

Normally distributed variables were evaluated using the Shapiro–Wilk test. Given their skewed distribution, quantitative data were expressed as medians (interquartile range, IQR). Comparisons between groups were made using the Mann–Whitney *U* test or Pearson's Chi-squared test, and the relationship between continuous variables was assessed by Spearman's correlation test.

Accuracy of skin AF as a measurement of interest to discriminate patients with FEV1 scores $\leq$ 80% of predicted from normal cases was evaluated using receiver operating characteristic (ROC) curve analysis and a complete sensitivity/specificity report. In addition, comparisons between area under the ROC (AUROC) of skin AF and HbA_{1c} were performed using the Hanley and McNeil test.

Stepwise multivariate regression analysis explored the variables independently associated with FVC and FEV1, including age, gender, body mass index (BMI), tobacco use (number of pack-years), HbA_{1c} and skin AF. Statistical significance was accepted at the level of $P < 0.05$. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0, software (IBM Corp., Armonk, NY, USA).

The main clinical characteristics of the study population are shown in Table 1. Skin AF was significantly higher in patients with T2D than in those with either prediabetes [2.5 (2.0–3.0) vs 1.9 (1.7–2.2) AU; $P < 0.001$] or no glucose abnormalities [1.9 (1.7–2.2) AU; $P < 0.001$]. No differences in skin AF levels were observed between the latter two groups. In addition, patients with T2D showed significantly lower FEV1 and FVC scores, and a greater prevalence of FEV1 scores < 80% than either prediabetes or non-diabetes subjects (Table S1; see supplementary materials associated with this article online). Those with prediabetes showed significantly lower FVC scores than those with no glucose abnormalities ($P = 0.046$).

When skin AGE deposition was evaluated according to ventilatory pattern, patients with respiratory (non-obstructive or obstructive) defects exhibited significantly increased skin AF in comparison to subjects with normal pulmonary function (all $P < 0.001$). When the entire study population was evaluated, positive correlations were found between skin AF and age, HbA_{1c}, tobacco packs/year and estimated glomerular filtration rate (eGFR) on univariate analysis (Table S2; see supplementary materials associated with this article online). In addition, a significant but negative correlation between skin AF and pulmonary parameters, such as FVC ($r = -0.114$, $P < 0.001$) and FEV1 ($r = -0.212$, $P < 0.001$), was observed. Moreover, these correlations became even stronger when only T2D patients were analyzed (FVC: $r = -0.453$, $P < 0.001$; FEV1: $r = -0.393$, $P < 0.001$).

ROC analysis revealed that the optimal cut-off point for skin AF was 2.05 AU: at this point, the AUROC was 0.614 (0.582–0.646), with a sensitivity of 53.5% and specificity of 63.3%. The percentage of subjects with FEV1 < 80% increased from 17.4% in those with skin AF < 2.05 AU to 27.6% in those with skin AF $\geq$ 2.05 AU ($P < 0.001$). These data indicate a twofold greater risk of having an abnormal FEV1 (mean difference: 1.9, 95% CI: 1.5–2.3; $P < 0.001$) compared with subjects with lower skin AF values. In addition, skin AF significantly improved the AUROC curve obtained with HbA_{1c} measurement [0.614 (0.582–0.646) vs 0.555 (0.521–0.589); $P = 0.014$]. Furthermore, stepwise multivariate regression analysis revealed that skin AF (along with gender, BMI, tobacco use and HbA_{1c}) was independently associated with predicted measures of FEV1 ($R^2 = 0.121$) and FVC ($R^2 = 0.122$) (Table S3; see supplementary materials associated with this article online).

To the best of our knowledge, this is the first-ever study of subjects without pulmonary disease to demonstrate that skin AGE deposition is related to a decrease in spirometric values and a larger percentage of abnormal ventilatory patterns. In addition, this negative association was more aggravated among patients with T2D.

AGE formation increases with age and is accelerated by chronic hyperglycaemia, chronic inflammation and oxidative stress [5]. Skin AF is also associated with several clinical variables (for example, age, creatinine clearance), lifestyle factors (smoking status, coffee consumption), and genetic polymorphisms [6]. Our present data from a large population are in concordance with those findings. As AGEs are mainly irreversibly linked to tissue proteins,

Table 1
Main clinical characteristics, metabolic data, pulmonary function and breathing pattern parameters in the study population according to glucose abnormalities.

	T2D patients	Prediabetes	Non-T2D patients
n	79	660	1170
Women, *n* (%)	39 (49.4)	393 (59.5)	567 (48.5)
Age (years)	61 (55–65)	59 (54–64)	57 (52–62)
Known T2D duration (years)	12 (8–15)	–	–
Body mass index (kg/m^2)	30.8 (27.8–35.6)	29.6 (26.9–33.2)	28.1 (25.3–31.4)
Current smoker, *n* (%)	18 (22.7)	155 (23.4)	387 (33.0)
Tobacco, *n*, (pack-years)	21.0 (15.0–42.8)	20.9 (10.1–34.8)	20.5 (9.0–32.0)
HbA_{1c} (%)	8.4 (6.7–9.6)	5.8 (5.7–6.0)	5.4 (5.2–5.5)
HbA_{1c} (mmol/mol)	67 (50–81)	40 (39–42)	36 (33–37)
Total cholesterol (mg/dL)	185 (159–213)	203 (182–229)	201 (180–227)
eGFR (mL/min/1.73 m^2)	90.0 (74.7–94.9)	95.8 (85.9–101.9)	97.1 (87.7–103.3)
Skin autofluorescence (AU)	2.5 (2.0–3.0)	1.9 (1.7–2.2)	1.9 (1.7–2.2)

Data are expressed as medians (IQR) or as *n* (%); T2D: type 2 diabetes; eGFR: estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

its accumulation is greater with slow turnover rates, as seen in subcutaneous tissue, lens and cartilage [5,6].

Similar to other cross-sectional studies, our present study has shown how patients with T2D exhibit a 13% decrease in FEV1 and 14% decrease in FVC of a theoretical value compared with non-diabetes subjects [1,2]. On this basis, it has been suggested that non-enzymatic glycosylation of pulmonary parenchymal proteins and chest wall cartilage may favor the development of less-compliant lung parenchyma and, thus, limit chest mobility, an underlying factor in the restrictive respiratory pattern described in T2D [1]. Our results, with skin AF as an independent risk factor for spirometric values, support the potentially deleterious impact of AGEs on pulmonary function.

The role of AGEs in the genesis and rapid progression of both macro- and microvascular chronic T2D complications has been suggested previously [7]. Likewise, descriptions of messenger RNA (mRNA) expression of AGE receptor (RAGE) by type-II alveolar epithelial cells are worthy of attention [8]. Indeed, AGE–RAGE interactions in the lungs might trigger pathophysiological cascades, leading to impaired pulmonary function through lung endothelial cell dysfunction, proinflammatory effects and cell apoptosis [8]. It is also worth mentioning that our data revealed that prediabetes has a negative impact on FVC in comparison to subjects with normal glucose metabolism but similar skin AF. This finding suggests that mechanisms (such as insulin resistance) other than AGE accumulation might be playing a primary role in initiating the lung impairment seen in T2D.

The involvement of AGEs in patients with COPD has also been previously evaluated, and skin AF was significantly higher in 202 patients with mild-to-very-severe COPD compared with 193 old and young healthy controls [3]. Similar results were also observed in a smaller group of patients, with skin AF proving to be a negative determinant of FEV1 even after adjusting for age, gender and pack-years of smoking [9]. In fact, our present study demonstrates that the negative correlation between skin AF and pulmonary function is not restricted to COPD, as the association was stronger among patients with T2D than in non-diabetes subjects.

Nevertheless, our study has a few limitations. First, it would have been of interest to compare skin AF data with plasma AGE concentrations. Second, as skin AF mainly provides information on AGEs linked to fluorescent proteins, the role of other compounds was not evaluated and, third, the cross-sectional nature of the study does not permit causality to be established.

In conclusion, the present study has provided the first clinical evidence that, in people with no known pulmonary disease, AGEs, as measured by skin AF, are correlated with a decline in spirometric values. The link was even stronger among patients with T2D, suggesting that the accumulation of AGEs in lung parenchyma and the chest wall may now be added to the mechanisms involved in the deleterious effects of T2D on lung function.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabet.2018.04.002.

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The 36% coefficient of variation for glucose proposed for separating stable and labile diabetes is clinically relevant: A continuous glucose monitoring-based study in a large population of type 1 diabetes patients

The relationship between haemoglobin A_{1c} (HbA_{1c}) and risk of micro- and macrovascular complications in patients with type 1 diabetes (T1D) has been well demonstrated, particularly by the Diabetes Control and Complications Trial (DCCT) [1] and Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study [2]. Unlike the long-term glucose assessment provided by the HbA_{1c}, glycaemic variability (GV) requires a comprehensive analysis of glycaemia that includes both glucose excursions and time factors. It is well established that tight glucose control increases the risk of hypoglycaemia [1].

Now, the development of continuous glucose monitoring (CGM), which enables monitoring interstitial glucose levels almost continuously, allows subsequent analyses of short-term glucose variability to be performed. The most-used within-day and between-day variability indices with CGM are the standard deviation (SD), coefficient of variation (CV; SD/mean glucose value), mean amplitude of glycaemic excursion (MAGE) and continuous overlapping net glycaemic action (CONGA). The most-used between-day GV index is the mean of daily difference (MODD), while other indices assess the risk of hypoglycaemia or hyperglycaemia [low blood glucose index (LBGI), high blood glucose index (HBGI) or both (Average Daily Risk Range, ADRR)]. Formulas for these indices are detailed in a recent review [3].

Yet, a growing problem for clinicians is that most of these indices are complex, with many interfering factors such as timing and type of meals. A recent study by Monnier et al. [4] concluded that a CV percentage (%CV) of 36 appears to be a suitable threshold to distinguish between stable and unstable glycaemia. The authors also emphasized the idea that the %CV is a pragmatic and easy tool that can be adjusted for mean glucose values, but does not depend on glucose levels. This 36% threshold has now been adopted as the primary metric to separate stable from unstable diabetes by the International Consensus on the Use of Continuous Glucose Monitoring [5].

Thus, the present study aimed to implement this %CV cut-off value in a large population of T1D patients, each of whom wore a professional-grade CGM device as a way to determine the impact of such stratification on glycaemic parameters as well as several alternative GV indices and the risk of hypo- and/or hyperglycaemia.

Our study retrospectively included 206 T1D patients who performed professional blinded ambulatory CGM for at least 3 days and up to 7 days (iPro2 CGM, Enlite sensor; Medtronic, Minneapolis, MN, USA) between 2011 and 2017. The iPro2 recorder digitally stores the average sensor reading every 5 min, and all subjects performed at least four capillary blood glucose tests per day to calibrate the CGM system.

These patients all presented with either repeated hypoglycaemia or persistent above-target HbA_{1c} levels. Age, body mass index (BMI), type of treatment (multiple daily injections or subcutaneous insulin infusions), diabetes duration and HbA_{1c} were determined for all patients at the time of CGM recording. All investigations were routinely performed at the diabetes outpatients clinic of the University Hospital of Lyon (France), and all procedures were in accordance with the Declaration of Helsinki.

Time spent in hypoglycaemia, and in and above the glucose target, were defined as the total duration of periods with glucose levels < 70 mg/dL, 70–180 mg/dL and > 180 mg/dL, respectively. A hypoglycaemic episode was defined as at least three consecutive measures < 70 mg/dL (for at least 10 min), and the estimated HbA_{1c} was determined using mean glucose values. Evaluated GV measures included SD, %CV, MAGE, CONGA (at 1 h and at 4 h), MODD, ADRR, LBGI and HBGI, which were determined from the CGM recordings using the original methods of assessment.

Values are presented as means ± SD or percentages. Statistical tests were two-tailed; for descriptive and exploratory analyses, a significance level of $P < 0.05$ was adopted. Two-group comparisons were conducted using Student's *t* test for data with normal distribution, and the Mann–Whitney U test for data with a skewed distribution pattern; chi-squared test was used for non-parametric data; and correlations between variables were calculated using Spearman's correlation (rho). Statistical analyses were performed using SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA).

A total of 206 T1D patients were retrospectively included in our study (Table 1). Mean age was 44.1 years, 45% were women, mean BMI was 25.2 kg/m^2, mean duration of diabetes was 21.0 years, 33% were treated by subcutaneous insulin pump, and mean HbA_{1c} was 8.2% ± 1.3 for the entire study population. CGM-derived glucose data and GV indices are detailed in Table 1. Mean glucose was 172 mg/dL ± 32 and estimated HbA_{1c} was 7.6% ± 1.1 for the whole of the study population.

Using Spearman's correlation, it was determined that the indices that correlated well with time spent in hypoglycaemia were the %CV (rho = 0.678) and LBGI (rho = 0.977), whereas the indices that correlated well with time spent in hyperglycaemia were SD (rho = 0.539), MODD (rho = 0.474), MAGE (rho = 0.448) and HBGI (rho = 0.946; Table S1; see supplementary materials associated with this article online).

Using the %CV cut-off of 36, the population was split into two subgroups (Table 1). Those with a %CV ≤ 36 (n = 49) were significantly older (48.8 ± 16) than those with a %CV > 36 (42.6 ± 14 years). Gender ratio, BMI and diabetes duration did not differ between the two subgroups. The proportion of patients treated by insulin pump was not significantly larger in the group with the lower %CV (38.7% *vs* 31.2%; P = 0.235), nor was the HbA_{1c} value (8.5 ± 1.4% *vs* 8.1 ± 1.4%; P = 0.07). Concerning glucose homoeostasis, the mean glucose value, estimated HbA_{1c} and time (%) spent in hyperglycaemia tended to be higher in the low %CV group, although statistical significance was not reached. The amount (%) of time spent on target (glucose 70–180 mg/L) was the same in both subgroups, whereas the amount (%) of time spent in hypoglycaemia and number of hypoglycaemic episodes were both significantly lower in the group with a %CV ≤ 36. All GV indices were significantly lower in the low %CV group except for HBGI. The proportion of time spent in