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Bronchiolitis in young female smokers

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KEYWORDS
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Summary
Background: Smoking is a growing concern among young women. However, the pulmonary effects of smoking in young female smokers in their 20's are unknown.
Objective: The purpose of this study was to determine whether young female smokers demonstrate smoking-related lung abnormalities such as bronchiolitis in their 20's.
Methods: We recruited young females (20–30 yr) from Izmir, Turkey; 29 smokers and 31 lifetime non-smokers. They were all asymptomatic. All subjects performed complete lung function measurements and underwent thoracic computed tomography (CT) scanning at suspended full inspiration using a Toshiba "Aquilion" multi-slice CT scanner. The CT images were analyzed using custom software (Emphylx-J) and published equations to calculate total lung volume, mean lung density, lung mass, and the extent of emphysema. CT images were also read semi-quantitatively for respiratory bronchiolitis and emphysema by 2 experienced chest radiologists. When there was substantial difference in scoring, a 3rd (independent) radiologist read the CT scans. Plasma biomarkers of smoking were also measured in these subjects.
Results: Although none of the subjects demonstrated emphysema on CT images, 41% of smokers (compared with only 15% of non-smokers) had evidence for respiratory bronchiolitis (with a score of 2 or more; $p = 0.0301$). There was a significant relationship between pack-years of smoking and the severity of respiratory bronchiolitis in smokers. Plasma interleukin

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(IL)-6 levels were also higher in smokers than in non-smokers ($p = 0.028$). Quantitative analysis for emphysema or airways disease on CT scans did not reveal any significant differences in the two groups with the exception of lung mass, which was higher in the smokers than in non-smokers. Lung function was similar between the two groups.
Conclusion and clinical relevance: Young female smokers in their 20's and 30's demonstrate CT changes consistent with respiratory bronchiolitis and elevated plasma IL-6 levels. They also have "heavier" lungs compared with lifetime non-smokers. These data indicate that pathologic changes of smoking occur early in young female smokers in the absence of demonstrable airflow limitation or symptoms. Public health efforts to curb smoking in young women are clearly needed to reduce the burden of smoking related lung disease in women.
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Introduction

There is a global epidemic of smoking-related lung diseases. Worldwide, smoking is responsible for nearly 5 million deaths annually.[1] In the Western World, the rates of chronic obstructive pulmonary disease (COPD) are increasing at a much faster rate in women than in men.[2] Alarmingly, women who smoke 20 cigarettes per day (i.e. 1 pack/day) are 60 times more likely to develop COPD than non-smoking females.[3] However, despite this information young people, especially women, continue to smoke at an alarming rate and most start to smoke in their teens or early 20's. In the US, for instance, the age group with the highest percentage of female smokers is between 20 and 30 years of age.[4] In this age group, many female smokers believe that they can stop smoking at a later age and avoid the adverse impact of cigarette smoke or that smoking modestly has no significant impact on health.[5] It is not known however whether smoking produces any demonstrable adverse effects in the lungs of young female smokers. In the early 1970's using data from resected lung tissue, Niewoehner and colleagues showed that the earliest pathologic feature of cigarette smoking in lungs of young male smokers was respiratory bronchiolitis, which could be detected by histology, decades before the development of other pathologic features of smoking-related lung disease such as emphysema and airway wall remodeling.[6] However, because lung function measurements were not performed in this cohort, it is not known whether the smoking-related bronchiolitis resulted in any demonstrable airflow limitation. Furthermore, Niewoehner's study included only heavy male smokers (average age: 25 years and average smoking history of 20 pack-years). Thus, the findings of this study may not be generalizable to young female smokers, who on average smoke fewer cigarettes per day (than their male counterparts) and have increased risk of bronchial hyperresponsiveness.[7] With the advent of multi-detector computed tomography (MDCT) and high spatial resolution algorithms, it is possible to detect early changes of smoking related lung injury that could only be diagnosed using invasive methods or in *ex vivo* lungs. The primary purpose of this study was to determine the effects of cigarette smoking in the lungs of young female smokers in their 20's. We hypothesized that very early signs of emphysema and/or small airways disease can be measured using quantitative CT in young women. To study this question we recruited young women, both smokers and lifetime non-smokers and compared their pulmonary function data with both quantitative analysis of CT scans and a visual assessment of the images.

Methods

Study participants

Young female volunteers, aged between 20 and 30 years were recruited in Izmir, Turkey through advertising on bulletin boards around university campus and nurses' dormitory (Ege University, Izmir, Turkey). Thus, all participants in this study were either university students or nurses employed at the university hospital. One group consisted of active smokers with at least 5 pack-years of smoking history (smoking group) and the other consisted of lifetime non-smokers (control group). To qualify for the study, the subjects had to be free of any significant respiratory symptoms (such as cough or dyspnea), did not have any pulmonary disorders (e.g. asthma, COPD, bronchiectasis or tuberculosis) or co-morbidities (e.g. diabetes, cardiovascular disorder), were not taking any prescription medications and were not part of any other research study. All participants provided written informed consent and the study was approved by the Research Ethics Board of Ege University.

Procedures

Following informed consent, the subjects underwent full lung function measurements using Sensormedics Vmax Spectra 22D spirometer in accordance with the recommendations of ATS/ERS[8] and thoracic computed tomography (CT) scanning. All CT images were obtained at full inspiration without the use of intravenous contrast media, using a Toshiba Aquilion 16 slice multi-detector row CT scanner (Toshiba Medial Systems, Tokyo Japan) and the following parameters: 120 kVp, 40 mAs and the images were reconstructed using contiguous 1 mm thick images (FC51 reconstruction kernel) and contiguous 5 mm thick images (FC11 reconstruction kernel). On the day of pulmonary function tests and CT imaging, blood samples were drawn from all participants for analysis of interleukin (IL)-6 and surfactant protein-D (SP-D) measurements using commercial assay kits (R and D Systems for IL-6 and Biovendor for SP-D) and methods previously described.[9] These proteins were chosen *a priori* because plasma IL-6 levels are strongly associated with adverse health outcomes in

smoking-related lung disease[10] and SP-D levels are associated with increased lung permeability.[11]

Qualitative image analysis

The 1 mm thick images were subjectively assessed by two thoracic radiologists, who were blinded to the group assignment of the participants, to determine the extent of emphysema and the burden of bronchiolitis. A third reader provided consensus in the setting of discordance. Emphysema was scored using a previously described scoring system as follows: none (0), trivial (1) mild (2), moderate (3), severe (4), or very severe (5). Bronchiolitis was scored using a quartile system according to Fleischner guidelines and the following scale: none (0), trivial (1), mild/moderate (2), or moderate/severe (3). Bronchiolitis was defined as centrilobular micronodules and patchy ground-glass opacity using Fleischner Glossary of terms.[12] The weighted kappa statistics for agreement of the bronchiolitis score was 0.842 (95% confidence interval, CI, 0.611−1.000). Centrilobular nodules were separated by several millimeters from the pleural surfaces, fissures, and interlobular septa and may be of soft-tissue or ground-glass attenuation (Fig. 1).

Quantitative image analysis

Quantitative analysis was performed in two steps using custom software (EmphylxJ, University of British Columbia, flintbox.com) as previously described.[13] First, emphysema was assessed using the 5 mm, low spatial frequency reconstructed CT images (FC11) by segmenting the lung parenchyma from the chest wall and large central blood vessels and by using a modified border-tracing algorithm with a prior position-knowledge algorithm. The segmented pixel area in each slice was summed and multiplied by the slice thickness to acquire the total lung volume. The mean CT attenuation of the lung in Hounsfield units (HU) was calculated and converted to a measure of density in g/ml by adding 1000 to the HU number and dividing by 1000. The mean density of the lung was then multiplied by the lung volume to estimate lung mass. The extent of emphysema, or low attenuation area (LAA), was defined as voxels with an attenuation value less than −950 HU and expressed as percent of the total lung volume. The apparent X-ray attenuation value at the lowest 15th percentile point of the distribution was also calculated. A "low attenuation cluster analysis" was used to estimate the size distribution of the low density regions within the lung. The inverse slope of the log−log relationship of the size of the clusters (number of contiguous voxels less than −950 HU) versus the number of clusters of that size is the power-law exponent (D). Individuals with diffuse small clusters of low density lung will have a steeper slope (i.e. greater D) than individuals with larger-sized low density regions.

Second, cross sectional airway dimensions were determined using the full-width at half maximum algorithm as previously described. Briefly, using the thin slice (1 mm) high spatial frequency reconstruction CT images (FC51) a random image was selected near the apex of the lung. From this start point, every 10th image was chosen and all airways that were cut in a reasonable cross section (long/short internal diameter 2.2 or less) were identified. Every 10th image was chosen to sample unique airways and on average 23 ± 12 airways per subject were measured (minimum = 4, maximum = 55). A seed point was placed in the lumen of the airway and the internal and external boundary of the airway wall were determined by casting radial lines from this seed point and finding the internal and external point at which the X-ray attenuation value along the line was half the maximum value within the wall. A standardized measurement of airway wall thickness was obtained to try to minimize sampling bias. The measurements of internal perimeter (Pi) were correlated with the square root of airway wall area (Aaw) for

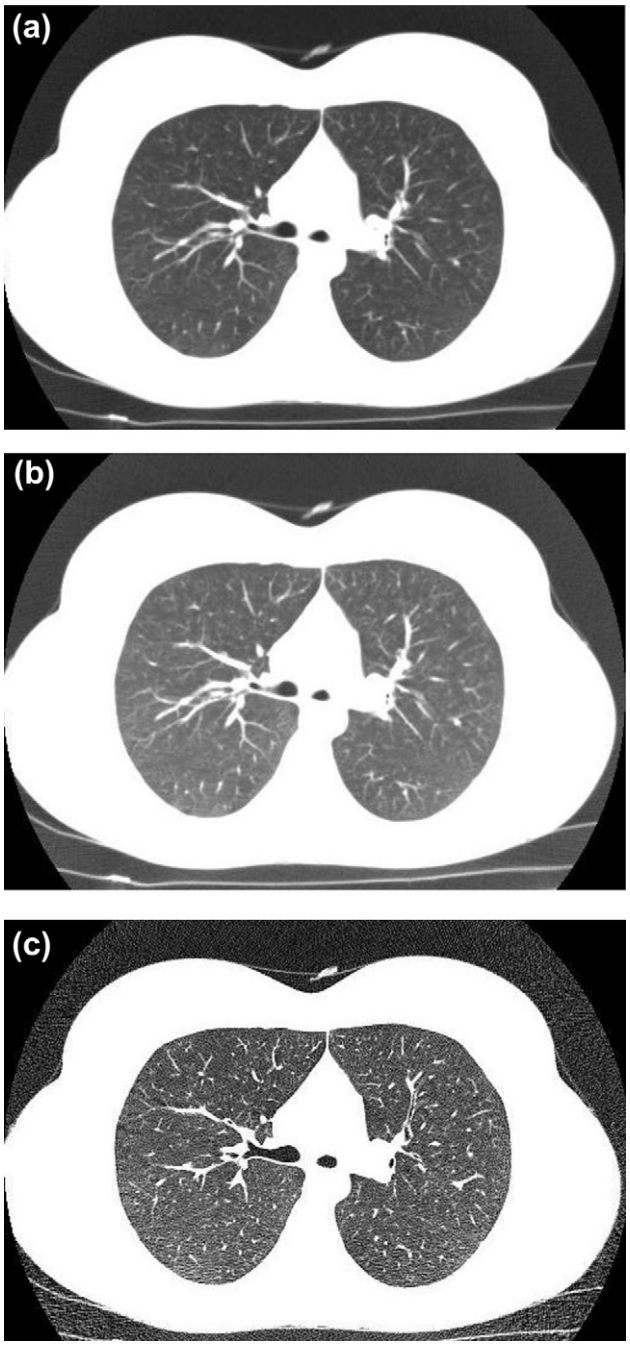


Figure 1 Representative MDCT images of respiratory bronchiolitis. (a) Shows control (no bronchiolitis). (b) Shows RB score of 1. (c) Shows RB score of 2 or more.

each subject individually. Using the resulting regression equation square root of the airway wall for an idealized airway with an internal perimeter of 10 mm (AWT-Pi10) for each subject was calculated.

Statistical analysis

Continuous variables between the smokers and controls were compared using a Student *t* test. For non-normally distributed variables (e.g. plasma IL-6 levels), a logarithmic distribution was used to transform the variables. Dichotomous variables were compared using a chi-square test with appropriate degrees of freedom. A two-tailed *p*-value less than 0.05 was considered significant. Based on a previous study, we estimated the SD of the bronchiolitis score to be 0.26.[14] With a sample size of 25 (in each group), we had >80% power to detect a mean difference score of 0.213 or greater between the smokers and non-smokers with respect to the bronchiolitis score. All analyses were performed using SAS version 9.2 (Carey, N.C.)

Results

There were 60 subjects in the study. Their mean age was 24.4 ± 3.1 (mean ± SD) years and mean body mass index (BMI) was 21.5 ± 3.3 kg/m^2. The clinical characteristics of the study participants according to their smoking status are summarized in Table 1. There was good balance in the baseline characteristics between the two groups except for BMI, which was larger in the smoking group compared to the control group ($p = 0.023$). Specifically, there were no significant differences in the lung function parameters between the two groups. No subjects had forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio less than 0.7, indicating significant airflow limitation.

There was no emphysema visually apparent in any of the subjects. However, there were significant differences in the mean bronchiolitis score between the two groups ($p = 0.019$). Twelve (41%) of the smokers group had bronchiolitis score of 2 or greater compared to only 5 (16%) in the control group (Fig. 2; $p = 0.0301$). In the smokers group, 15 (52%) of the subjects did not have any radiographic evidence of bronchiolitis, while in the control group 26 (84%) did not have bronchiolitis. There was a significant relationship between the respiratory bronchiolitis score and pack-years of smoking history with an increment of 10 pack-years leading to 0.7 unit rise in the respiratory bronchiolitis score ($p = 0.0296$). Fig. 3 demonstrates the relationship between pack-years of smoking and the respiratory bronchiolitis score.

Although the quantitative analysis did not reveal any significant differences in lung volume, density or extent emphysema, measured using either the threshold analysis (%LAA) or the lowest 15th percentile value between the two groups, the calculated lung mass of the smokers was significantly greater than that in the control group. Moreover, using a low attenuation cluster analysis, smokers demonstrated increased D values suggesting less heterogeneity in the size of airspaces. There were no significant differences in any of the airway wall measurements.

Plasma IL-6 levels were increased in the smokers' group than in the control group (Fig. 3; $p = 0.028$). Plasma SP-D levels, however, did not differ significantly between the two groups ($p = 0.259$) (see Table 2). Neither plasma IL-6 (Spearman rho = 0.23; $p = 0.138$) nor SP-D levels (Spearman rho = 0.05; $p = 0.740$) were significantly related to the bronchiolitis score.

Table 1 Clinical characteristics of smokers and non-smokers.

Variables	Non-smokers ($n = 31$)	Smokers ($n = 29$)	*P*
Age (years)	23.8 ± 2.63	24.9 ± 3.5	0.186
BMI (kg/m^2)	20.6 ± 2.8	22.5 ± 2.9	0.023
Smoking history (pack-years)	—	8.1 ± 4.4	—
Age at smoking initiation	—	16.8 ± 2.8	—
FEV_1 (% of reference value)	92.4 ± 13.2	94.4 ± 11.1	0.526
FEV_1 (ml)	3079 ± 486	3099 ± 385	0.861
FVC (% of reference value)	93.4 ± 14.0	96.3 ± 11.8	0.382
FVC (ml)	3605 ± 607	3673 ± 472	0.628
FEV_1/FVC (%)	86.7 ± 5.7	84.7 ± 6.7	0.221
DLCO (% of reference value)	84.0 ± 15.5	84.1 ± 12.4	0.985

BMI = body mass index.
DLCO = diffusing capacity of the lung for carbon monoxide.
FEV_1 = forced expiratory volume in one second.
FVC = forced vital capacity.

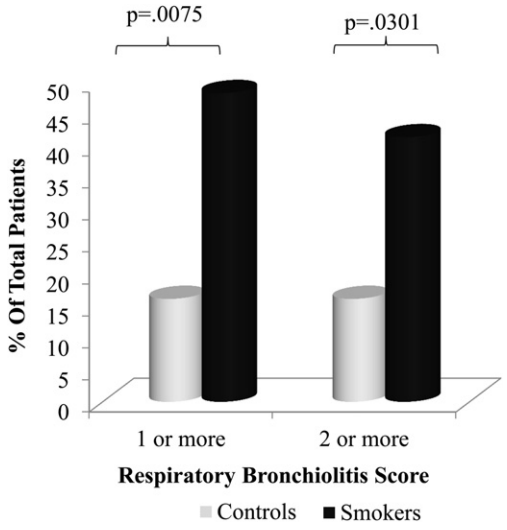


Figure 2 The relationship of smoking status to the occurrence and severity of bronchiolitis detected on MDCT. *P* values determined using a chi-square test.

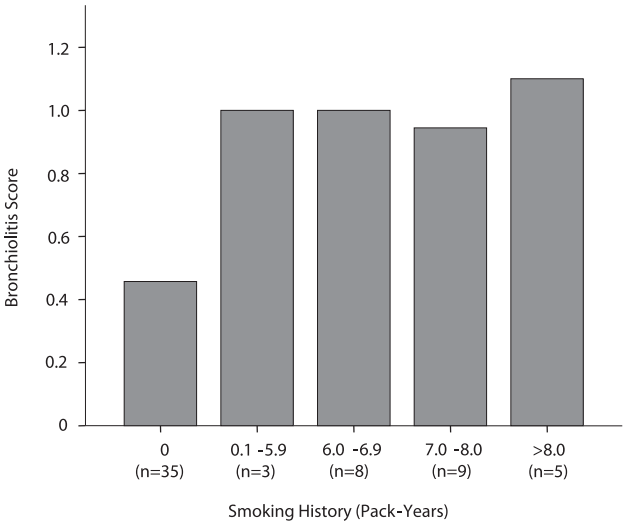


Figure 3 The relationship of the respiratory bronchiolitis score to pack-years of smoking.

Discussion

The most important finding of the present study was that young female smokers in their 20's have radiographic evidence of small airway disease (i.e. bronchiolitis), "heavier" lungs and elevated plasma IL-6 levels compared to similar aged non-smoking women. Importantly, none of the smoking women had radiographic evidence of emphysema. Together, these data suggest smoking related changes are first notable in the airways (and not in the parenchyma), occur very early in life and that they can be detected using MDCT. We also found that none of the female smokers had developed airflow limitation on spirometry. These data suggest that in young smokers spirometry is insensitive (and unlikely to be clinically useful) in detecting smoking-related lung changes. Whether plasma biomarkers such as IL-6 would be useful in this setting is uncertain.

Our study findings are consistent with those of Niewoehner and colleagues who demonstrated in 39 young men (mean age 25 years and 20 mean pack-years of smoking) that the most consistent pathologic finding among smokers was respiratory bronchiolitis.[6] Indeed, in this study, all 19 young male smokers had histologic evidence of respiratory bronchiolitis but only 5 out of 20 non-smokers demonstrated this feature. However, no women were included in this study and all the subjects were heavy smokers with an average smoking history of 25 $\pm$ 7 pack-years (mean $\pm$ SD). Thus, we extend the findings of Niewoehner et al. by demonstrating radiographic evidence of respiratory bronchiolitis in young female smokers who had on average only 8 $\pm$ 4 pack-years of smoking.

There were no large quantitative differences in CT density between the two groups of subjects. However, smokers demonstrated "heavier" lungs, which is in line with other published studies that have shown significant changes in lung density before and following smoking cessation. Investigators in Copenhagen, for instance, have reported that there is a rapid decrease in lung density, assessed using the lowest 15th percentile, following smoking cessation and a similar decline in subjects receiving inhaled corticosteroids.[15,16] These authors suggested that a change in the inflammatory response may have been responsible for these small but significant changes in lung density. We were not able to demonstrate a difference in the lung density at the lowest 15th percentile point, and this may be due to the fact that these women were young and most of their lung density fell within the normal range. However, there was a trend for an increased mean lung density which did reach significance when combined with the lung volume to calculate lung mass.

Given the location of the airway lesions (in the small airways), it is not surprising that none of the subjects in our study demonstrated airflow limitation. Small airways are often referred to as the "quiet zone", which because of its large surface area can become extensively diseased and still not lead to symptoms or significant airflow limitation.[17] Although in the present study, we did not re-image the subjects following smoking cessation, previous studies suggest that the small airway changes related to cigarette smoking are partially reversible in about two-third of smokers. Similarly, smoking cessation appears to reduce plasma IL-6 levels.[18]

There were some limitations to the present study. First, this was a cross-sectional study. As such, the natural history of the small airway changes related to cigarette smoke is unknown. However, previous studies suggest that over time, permanent remodeling takes place in the small

Table 2 Radiographic findings in young female participants.

Variables	Non-smokers	Smokers	*P*
Total lung volume (L)	4123 $\pm$ 791	4246 $\pm$ 757	0.481
Total lung mass (g)	**535 ± 91**	**592 ± 110**	**0.032**
Mean lung density (g/mL)	0.134 $\pm$ 0.030	0.144 $\pm$ 0.034	0.333
D (-950)	**1.91 ± 0.44**	**2.14 ± 0.43**	**0.016**
Low attenuation area (%)[b]	12.2 $\pm$ 15.1	9.1 $\pm$ 15.1	0.446
15% percentile cutoff (HU)	$-$984 $\pm$ 30	$-$972 $\pm$ 35	0.284
Pi_{10} (mm)	2.68 $\pm$ 0.36	2.72 $\pm$ 0.34	0.846
RB score	0.355 $\pm$ 0.829	1.035 $\pm$ 1.172	0.019
IL-6 (pg/ml)[a]	1.54 $\pm$ 0.655	2.22 $\pm$ 0.458	0.028
SP-D (ng/ml)[a]	55.6 $\pm$ 0.763	72.1 $\pm$ 0.998	0.259

HU = Houndsfield unit.
RB = Respiratory Bronchiolitis.
IL-6 = interleukin-6.
SP-D = surfactant protein D.
D = inverse slope of the log–log relationship of the size of the clusters (number of contiguous voxels that are inflated beyond the predicted value for maximum lung inflation for that individual) versus the number of clusters of that size is the power-law exponent.
Significant row comparisons have been bolded.
[a] Results reported as geometric mean $\pm$ coefficient of variation.
[b] Percentage of the lungs with a density less than $-$950 Hounsfield Units.

airways, leading to significant airflow limitation and symptoms.[19,20] Second, owing to the study design, we cannot fully assign causality. However, a recent study by McDonough et al. suggests that the pathological process in chronic obstructive pulmonary disease (COPD) begins in the small airways and spreads distally into lung parenchyma, causing tissue destruction and emphysematous changes.[21] Third, we did not have histological verification of the CT findings. Thus, we cannot be absolutely certain that the CT based diagnosis of respiratory bronchiolitis was indeed true. However, previous studies have shown excellent correlation between CT and histologic findings of respiratory bronchiolitis,[22,23] providing some reassurances.

In summary, the present study indicates that young female smokers with a very modest smoking history demonstrate CT findings consistent with respiratory bronchiolitis and systemic inflammation in the absence of any lung function changes. These data indicate that the adverse effects of smoking occur at a very young age in women and highlight the importance of early intervention and education to reduce global smoking rates in young women.

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Conflict of interest statement

DDS has received research funding from AstraZeneca and received honoraria for speaking engagements from GlaxoSmithKline, Merck, Takeda, and Grifols, He has also sat on advisory boards for Novartis, Merck and Takeda over the past 3 years.

HC received $4800 in the years 2008–2012 for serving on the steering committee for the ECLIPSE project for GSK. In addition HC was the co-investigator on two multi-center studies sponsored by GSK and has received travel expenses to attend meetings related to the project. HC has three contract service agreements with GSK to quantify the CT scans in subjects with COPD and a service agreement with Spiration Inc to measure changes in lung volume in subjects with severe emphysema. HC has received a fee for speaking at a conference and related travel expenses from AstraZeneca (Australia). HC was the recipient of a GSK Clinical Scientist Award in 2010.

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