Official Journal of the Asian Pacific Society of Respirology
Respirology

CORRESPONDENCE

Serum YKL-40 in workers at an indium-tin oxide production facility

To the Editors:

We read with great interest the study by Bonella *et al.*, in which the authors evaluated the utility of serum YKL-40 as a biomarker for pulmonary alveolar proteinosis (PAP).[1] They found that YKL-40 correlated with respiratory impairment and disease outcome. The study subjects had primary autoimmune PAP, characterized by elevated GM-CSF antibodies. Less commonly, secondary PAP can occur in association with immunosuppression, haematological disorders and occupational inhalation exposure to certain dusts or fumes. GM-CSF antibodies are generally within the normal range in cases of secondary PAP, although the role of GM-CSF antibodies in secondary PAP due to occupational dust exposure remains an area of active inquiry.[2]

Indium lung disease is a potentially fatal lung condition that is characterized by PAP, emphysema and/or fibrosis in workers exposed to indium-tin oxide (ITO) and/or other indium-containing compounds.[3] We reported two cases of PAP in workers at a US ITO production facility in 2010, one of whom had elevated GM-CSF antibodies and the other was not tested.[4] Xiao *et al.* reported a case of PAP in an indium-exposed worker who had GM-CSF antibodies within the normal range.[2]

In 2012, we evaluated the current workforce at the US ITO production facility where the PAP cases had occurred.[3] In addition to symptoms and lung function, we assessed a number of biomarkers. No clinical cases of PAP or indium lung disease were identified in the 87 workers evaluated; however, plasma indium concentrations were associated with respiratory symptoms, decreased spirometric parameters and increased KL-6 and SP-D, which are biomarkers of interstitial lung disease. KL-6 and SP-D were elevated in 58% and 10% of workers, respectively. GM-CSF and LDH were not elevated in any of the workers tested. Interestingly, YKL-40 was elevated in 19% of workers, but was not correlated with plasma indium. We repeated the evaluation of current workers in 2014. Median YKL-40 from 2012 to 2014 evaluations was 57 ng/mL (mean: 80; range: 20–590 ng/mL).

In light of the study by Bonella *et al.*, we revisited our 2012 and 2014 data to evaluate relationships between YKL-40 and other biomarkers as well as lung function parameters in more detail (Table 1). Although Bonella *et al.* found a positive correlation with LDH and an inverse correlation with diffusing capacity of the lung for carbon monoxide (DL_{CO}), we found that YKL-40 did not correlate well with any biomarker or lung function parameter we tested. There was a weak correlation between YKL-40 and C-reactive protein (CRP). YKL-40 was higher in current or former smokers than never smokers (101 ng/mL vs 61 ng/mL; $P = 0.01$). We found no difference in YKL-40 by gender. Unlike in the study by Bonella *et al.*, we did observe a significant positive correlation between YKL-40 and age.

Table 1 YKL-40 correlations with other biomarkers, lung function, plasma indium and age in workers at an ITO production facility during 2012–2014

	Spearman's ρ	*P*-value
GM-CSF antibodies (2012 only)	0.08	ns
LDH (2012 only)	0.19	ns
CRP (2012 only)	**0.33**	**0.002**
KL-6	0.13	ns
SP-D	0.01	ns
$\%FEV_1$	–0.08	ns
%FVC	0.01	ns
FEV_1/FVC	–0.15	ns
$\%DL_{CO}$	–0.11	ns
$\%V_A$	–0.11	ns
Plasma indium	0.02	ns
Age	**0.24**	**0.03**

n = 101 and Includes workers from both 2012 and 2014 evaluations; 2014 results were used for workers who participated in each evaluation.

CRP, C-reactive protein; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GM-CSF, granulocyte macrophage colony-stimulating factor; ITO, indium-tin oxide; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; SP-D, surfactant protein-D; V_A, alveolar volume.

Our study population differed substantially from that of Bonella *et al.*[1] We surveyed healthy workers potentially at risk for secondary PAP following occupational ITO exposure, whereas Bonella *et al.*[1] surveyed patients with primary autoimmune PAP. However, the lack of significant associations between indium exposure and YKL-40, GM-CSF and LDH is noteworthy, and in contrast to the utility of KL-6 and SP-D in this worker population.

R. Reid Harvey, DVM, MPH Brie M. Hawley, PhD, MS
M. Abbas Virji, MSc, ScD and
Kristin J. Cummings, MD, MPH
[1]*National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, WV, USA*

Correspondence: R. Reid Harvey, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, 1095 Willowdale Road, Mailstop H2800, Morgantown, WV 26505, USA. Email: iez1@cdc.gov

doi: 10.1111/resp.13236

Disclosure statement

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health (NIOSH).

REFERENCES

1 Bonella F, Long X, He X, Ohshimo S, Griese M, Guzman J, Costabel U. Serum YKL-40 is a reliable biomarker for pulmonary alveolar proteinosis. *Respirology* 2017; **22**: 1371–8.

2 Xiao YL, KF X, Li Y, Li Y, Li H, Shi B, Zhou KF, Zhou ZY, Cai HR. Occupational inhalational exposure and serum GM-CSF autoantibody in pulmonary alveolar proteinosis. *Occup. Environ. Med.* 2015; **72**: 504–12.

3 Cummings KJ, Virji MA, Trapnell BC, Carey B, Healey T, Kreiss K. Early changes in clinical, functional, and laboratory biomarkers in workers at risk of indium lung disease. *Ann. Am. Thorac. Soc.* 2014; **11**: 1395–403.

4 Cummings KJ, Donat WE, Ettensohn DB, Roggli VL, Ingram P, Kreiss K. Pulmonary alveolar proteinosis in workers at an indium processing facility. *Am. J. Respir. Crit. Care Med.* 2010; **181**: 458–64.

From the Authors:

We would like to thank Harvey *et al*. for their interest in our work and for measuring YKL-40 in their cohort of workers at an indium-tin oxide (ITO) production facility, potentially at risk to develop secondary pulmonary alveolar proteinosis (PAP).

First, it should be noted that serum YKL-40 levels found in these ITO-exposed workers are similar to those described in healthy subjects in previous reports.[1–4] An important aspect is that these ITO-exposed workers did not suffer from PAP. In our PAP cohort, the mean YKL-40 serum level was sevenfold higher than in our healthy cohort. These high values may explain why correlations are seen only in PAP and not in healthy individuals, such as in the ITO-exposed workers.

Moreover, in regard to the lack of correlation with the decline in lung function, the findings by Harvey *et al*. are in contrast to what has been observed in the general adult population. In a multicentre analysis of 7325 measurements in 1058 subjects from the general population with normal spirometry (78%) or slight abnormalities (22%), Guerra *et al*. found that serum YKL-40 levels were linked to lung function deficit (both forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC)) and decline over time, particularly in smokers.[3] In addition, an inverse correlation with diffusing capacity of the lung for carbon monoxide (DL_{CO}) has been reported for sarcoidosis,[4] idiopathic pulmonary fibrosis (IPF)[5] and hypersensitivity pneumonitis (HP)[2] patients.

Similar to Harvey *et al*., we also found a weak correlation ($r = 0.264$, $P < 0.05$) of serum YKL-40 with age in patients affected by HP,[2] and Kruit *et al*. found that this correlation could explain 5% of the variation of this biomarker in serum.[4] That we did not find such a correlation in our patients with autoimmune PAP can be explained by the fact that they are relatively homogeneous in age (40–50 years old), similar to our healthy controls.

In addition, we observed the correlation of serum lactate dehydrogenase (LDH) with YKL-40 only in PAP and HP patients[2] but not in healthy controls, subjects who had normal LDH serum values similar to the ITO-exposed workers.

Finally, we want to underscore that all our predictive models based on YKL-40 cut-off values have been corrected for age, gender, BMI, smoking history, steroid therapy, disease type, baseline FVC, DL_{CO} and serum LDH as covariates, in order to avoid interferences, which could have been missed by testing single correlations.

Francesco Bonella, MD Ulrich Costabel, MD and on behalf of all co-authors

[1]*Interstitial and Rare Lung Disease Unit, Ruhrlandklinik, University of Duisburg-Essen, Essen, Germany*

Correspondence: Francesco Bonella, Interstitial and Rare Lung Disease Unit, Ruhrlandklinik, University of Duisburg-Essen, 45239 Essen, Germany. Email: francesco.bonella@ruhrlandklinik.uk-essen.de

REFERENCES

1 Bonella F, Long X, He X, Ohshimo S, Griese M, Guzman J, Costabel U. Serum YKL-40 is a reliable biomarker for pulmonary alveolar proteinosis. *Respirology* 2017; **22**: 1371–8.

2 Long X, He X, Ohshimo S, Griese M, Sarria R, Guzman J, Costabel U, Bonella F. Serum YKL-40 as predictor of outcome in hypersensitivity pneumonitis. *Eur. Respir. J.* 2017; **49**: 1501924.

3 Guerra S, Halonen M, Sherrill DL, Venker C, Spangenberg A, Carsin AE, Tares L, Lavi I, Barreiro E, Martinez-Moratalla J *et al*. The relation of circulating YKL-40 to levels and decline of lung function in adult life. *Respir. Med.* 2013; **107**: 1923–30.

4 Kruit A, Grutters JC, Ruven HJ, van Moorsel CC, van den Bosch JM. A CHI3L1 gene polymorphism is associated with serum levels of YKL-40, a novel sarcoidosis marker. *Respir. Med.* 2007; **101**: 1563–71.

5 Furuhashi K, Suda T, Nakamura Y, Inui N, Hashimoto D, Miwa S, Hayakawa H, Kusagaya H, Nakano Y, Nakamura H *et al*. Increased expression of YKL-40, a chitinase-like protein, in serum and lung of patients with idiopathic pulmonary fibrosis. *Respir. Med.* 2010; **104**: 1204–10.