

Short Communication

Clinical laboratory testing for smoking toxicity: implications for early identification of respiratory diseases

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ABSTRACT

Smoking toxicity has short and long term clinical effects and also leads to organ damage. However, clinical assessment in the context of early identification of smoke toxicity by evidence-base pathology is yet to be practiced. The present study was aimed to assess the knowledge and practice of health practitioners regarding clinical laboratory testing of smoking toxicity, with a view to generate a debate on why and how to test. In this pilot study, various health practitioners and students were asked via interviews about laboratory testing of smoking toxicity. There is considerable dismissal of 'why' to test and up 57% responded that it was unnecessary. However, there is general opinion that laboratory routine tests can be used to identify toxicity. It appears that there is a gap between knowledge and practice of clinical laboratory testing of cigarette toxicity. Students and health practitioners have the knowledge on smoke toxicity but this requires articulation into evidence-base pathology for early identification and intervention of subclinical pathology in smoking toxicity, especially before noticeable organ damage.

Key words: Cigarette smoke toxicity, Early identification, Laboratory methods, Pathology evidence base

INTRODUCTION

Cigarette smoking is a risk factor for many diseases including cancer, cardiovascular complications and respiratory diseases. Smoking is one of the factors in risk assessment of heart disease as well as death and in diabetes progression.¹ With particular interest on respiratory diseases, cigarette smoke and its extracts are associated with airway pathology due to destruction of alveolar epithelial cells, cigarette smoke is a risk factor for emphysema and bronchitis, while the mechanisms involve oxidative stress.²⁻⁷ The clinical symptoms of tobacco toxicity include clinical features such as dizziness, malaise, nausea and vomiting, bradycardia, dilated pupils as well as organ damage.⁸ Assessment of cigarette toxicity by mere count of number of cigars is

inaccurate because there are differences in metabolism due to ethnicity and method of smoking.⁹ Hence, assessment of nicotine metabolism is integral to nicotine dependency treatment programs; where zero level of nicotine metabolites and anabasine are indicative of abstinence from tobacco products.¹⁰

The metabolites such as nicotine, cotinine, trans-3'-hydroxy cotinine, nor nicotine and anabasine in urine, serum, and plasma can be tested using liquid chromatography-tandem mass spectrometry.¹¹ Biomarkers of nicotine and its metabolites can also be measured by spectrophotometric methods, immunoassays, gas chromatography, high performance liquid chromatography and liquid chromatography-tandem mass spectrometry.^{11,12}

While the toxic effects of cigarette toxicity are established, what is probably an issue is early identification of subclinical pathophysiology that has a measurable index as well as evidence base that quitting smoking could improve such subclinical pathology. Given this premise, the objective of this study is to determine the knowledge, attitude and practice of healthcare practitioners; through seven medical laboratory science students on clinical placement. The students were also asked to draw conclusions as comments to responses pooled.

METHODS

Design and setting

Akin to population based cross sectional questionnaire survey, this study adopted a ‘practitioner based face-to-face survey’.¹³ The research setting was Charles Darwin University Medical Laboratory Science clinical placement 2013.

The survey’s questionnaire comprised three open-ended items to ascertain:

- if the clinical laboratory performs tests to demonstrate pathology evidence-base for cigarette toxicity – e.g. as implicated in cancer, heart disease, etc;
- if cigarette toxicity could be tested in the clinical pathology setting;
- why ‘pathology evidence-base for cigarette toxicity’ is not assessed in the clinical diagnostic laboratories.

Seven 3rd year Bachelor of Medical Laboratory Science students of Charles Darwin University on clinical placement each interviewed different healthcare practitioners comprising laboratory scientific officers, pathologists, rehabilitation and psychiatry staff. The students were asked to interview at least two professionals, one of which must be a scientist.

Ethical compliance

This study was performed as research and teaching nexus in a clinical placement setting and the identities of interviewees were unrecorded, except for the profession. The interviews were verbal and responses were written out and submitted through a discussion forum created for the purpose. The students also gave opinions as respondents after the interviews, anonymously through the discussion forum.

Expected outcome

This was a small sample random opinion poll. It is known that cigarette smoke is toxic and it is a risk factor for several pathologies including respiratory diseases but there is yet to be established routine laboratory testing for

cigarette toxicity. What is unknown and the expected outcome of the survey is the opinion of healthcare professionals regarding ‘clinical laboratory testing for smoking toxicity’. Table 1 shows a summary of biomarkers that could be applicable to cigarette smoke toxicity testing. The expected outcome will include the opinion of respondents regarding these biomarkers (Table 1).

Table 1: Handy tests and applicability to smoke toxicity testing.

Handy lab tests	Index	Expectation
Full blood count ¹⁴⁻¹⁷	WBC	Leucocytosis
	HCT//RBC	Raised
	MCH//MCHC	Reduced
Liver function	Plasma protein	Normal or reduced
	Albumin	Normal or reduced
	ALP//GGT ^{18,19}	Raised
Renal function	ALT//AST ¹⁹	Varied
	GFR ^{20,21}	Varied
Lipid profile ²²	Proteinuria	Varied
	HDL	Reduced
Other tests	Other indices	Varied
	Folic acid ²³	Reduced
	Whole blood viscosity ^{††}	Raised or normal
	Sputum microscopy	Varied: normal to bloody and mucopurulent
	Bronchoalveolar lavage ²⁴	Eosinophilic pneumonia

††Smoking could raise WBV by increasing RBC, but decreases plasma proteins level.^{14,25}

We have previously demonstrated increased WBV, which was associated with RBC morphological changes. Such changes include abnormal RBC morphology and reduction in biconcave shape and this is attributable to the action of reactive oxygen species that damage the lipid bilayer by peroxidation and oxidation of cytoskeletal proteins.^{26,27} Therefore, hyperviscosity is also likely to be contributed to by the RBC becoming less deformable due to the action of oxygen free radicals. It is unlikely the low protein level could negate the raising effect of polycythaemia. Smoke-induced hypoproteinaemia can occur only in association with increased glomerular filtration rate.²¹ Therefore, hyperviscosity is expected more often than not.

RESULTS

Responses from the seven students based on their surveys. All seven scientists and the interviewed pathologists responded that ‘no’ to first question. The summary of common answers to the 2nd and 3rd questions is present (Table 2); as well as summary of

reasons argued ‘against’ and ‘for’ cigarette smoke toxicity testing (Table 3).

Discussion with pathologists on ‘How cigarette toxicity could be tested in the clinical pathology’ indicated that carboxyhaemoglobin can be tested to indicate carbon monoxide exposure from smoking. Arterial blood gas tests would show a compensated or uncompensated acidosis state from chronic obstructive pulmonary disease

caused by chronic smoking, as a measure of toxic damage to the patient. Electrolytes disturbances such high plasma potassium levels could also suggest acidosis. The symptoms of tobacco toxicity are non-specific hence a panel of tests such as full blood count, liver function tests, electrolytes, urea and creatinine would be required. There is no specific test for cigarette toxicity in histopathology, but for lung damage.

Table 2: Common answers to the survey questions indicating dismissive responses.

SN	Response to 2 nd question [†]					Response to 3 rd question [‡]	
Scientist (n = 7)	No		Yes			No client, cost inefficient, needs special equipment, test specificity	
Pathologist (n = 5)	Yes	No	Yes	*	Yes	*	Carboxyhaemoglobin, blood gas, serum electrolytes, FBC, No specific test for cigarette toxicity in histopathology
Pharmacist (n = 2)	*		Yes	Yes		Test kits are available; salivary & urine cotinine	
Rehab/Psychiatry (n= 2)			Yes	*		Lung function & CO breath tests; urine nicotine	

[†]If cigarette toxicity could be tested in the clinical pathology setting; [‡]why ‘pathology evidence-base for cigarette toxicity’ is not assessed in the clinical diagnostic laboratories; *No opinion polled.

Table 3: Reasons adduced against/for cigarette smoke toxicity testing.

Five reasons for and against testing	
Potential tests for	Against
Arterial blood gas for acidosis of COPD	Lack of specific test
Carboxyhaemoglobin indicates CO exposure	Lack of demand
Lung function//breath test	Pathology lab not involved in tobacco rehabilitation
Routine biochemistry & haematology for inflammation	Result may be counter productive
Urine test for anabasine and/or cotinine	Specialized equipment and staff training required

Discussion with a medical laboratory scientist on why testing for cigarette toxicity it is not performed in the laboratory indicated that although it could; it was not done since their laboratory did not have clients involved in tobacco rehabilitation programs that require such test; adding that it is cost inefficient to maintain quality assurance and quality controls for a test that will rarely be requested. Another medical laboratory scientist expressed that testing for the cigarette toxicity would require specialized equipment and staff training. A biochemist noted that lack of demand for testing and lack of specific test for cigarette toxicity were barriers in clinical biochemistry.

Further, a rehabilitation staff member advised that one of the best ways to show damage by cigarette smoking is by lung function tests and carbon monoxide breath tests. The former allows the patient to see a graphic display of her/his lung function. The rehabilitation staff member cautioned that measuring nicotine metabolites and finding that the patient can smoke twice as many cigarettes before reaching the same level of toxicity as another patient of different ethnicity, may be counterproductive.

Others participants noted that in the laboratory could analyse e.g. urine samples for nicotine and its breakdown products. Anabasine is can be tested for and a positive test would indicate active exposure to nicotine; passive smokers would have a negative result. The participant noted that the excretion of the metabolite the body takes around 2 weeks hence can be used to indicate abstinence of more than 2 weeks.

A pharmacist advised that test kits are available in pharmacies and they measure cotinine, which indicates recent tobacco use. The participant noted that cotinine is measureable in the urine and saliva, 4-7 days following the last use of tobacco depending on the test deployed and the rate of nicotine metabolism by the person being tested and the results are available within 5 minutes.

DISCUSSION

To test or not to test: a brief debate

It is submitted by various respondents that laboratory testing (a) such as lung function tests, arterial blood

gases, sputum microscopy can be useful in diagnosing cigarette toxicity and (b) assessment of toxicity would be beneficial as evidence of smoking exposure. Nicotine metabolites can be tested for in body fluids such as blood, saliva or urine and interestingly such tests are done in research settings, but can be performed at home since point-of-care tests are available in pharmacy stores.^{10,11} Perhaps, the debate is; if testing for cigarette toxicity can be done at home, why is it not available in the laboratory, where better quality assurance and interpretation of results can be provided. Cigarette toxicity testing is helpful for instance in assessing patients scheduled for surgery or to establish organ transplant eligibility due to increase risk in delayed healing time, infection and thrombosis in nicotine users.²⁸

Possibly, the responses that were dismissive of the need for laboratory test forgot or ignored the concept of evidence-base pathology for toxicity i.e. the importance of pathology evidence base to demonstrate clinical or subclinical process that may be due to cigarette or other forms of smoking. Based on responses from practitioners, 4/7 students concluded that testing for cigarette smoking toxicities or tobacco metabolites seems to be unnecessary because:

- It is not the level of nicotine that is in the body, it is whether that level causes them to become symptomatic.
- Though, smoking leads to adverse consequences, it does not influence daily performance at work or in everyday situations (for example compared to alcoholism) apart from time lost during “smoking breaks”, so there seems to be little need for such tests. Otherwise, in cases of complications, histology section may show smoking cigarettes effects, which could thereby be related to the disease.
- It is not necessary to assess the nicotine and its metabolites since nicotine and cotinine metabolism is affected by various factors including race, age, gender, diet and pregnancy. Furthermore, due to short half-life of nicotine and cotinine, the plasma/urine level only can reflect short-term exposure to tobacco.
- Testing for nicotine and its metabolites as part of dependence/abstinence program is unnecessary if the intention is to support an individual to quit. Individuals do not need a watchdog as part of dependency treatment programs to document abstinence.

Several respondents had the common reasoning that the level of nicotine and its metabolites in the system would not necessarily correlate to an individual’s presenting symptoms as there is variation in the activity of nicotine metabolism between individuals; citing for instance that most long term smokers do not develop lung cancer. Such opinions miss the fact that hyperlipidaemia is asymptomatic hence lipid profile is performed as part of

screening for early identification and intervention of heart disease risk.

One of the responses was that there is no specific test for cigarette toxicity in histopathology, but for lung damage. In our opinion, histopathological assessment involving biopsy would be too invasive. Perhaps, haemoximetry are quite sophisticated now, but give a lot of information about lung function and may even be able to identify subclinical pathology in smokers. There is the general opinion that smokers do not need a watchdog, or that the health hazards of cigarette and smoking are known and health workers recommend that the patient quits due to known correlation between smoking and a number of diseases. Perhaps, the question could be ‘Where is the pathology based evidence for early identification of health risk? – that is, to convince the smoker that some deleterious effect is occurring at subclinical level’.

There is bound to be some pathophysiological processes that would occur prior to the overt manifestation of CVD, in a smoker. For instance, cigarette smoking causes a build-up of carboxyhaemoglobin increases whole blood viscosity, which is a vasculopathy.¹⁴

Therefore, it is plausible that laboratory determination of WBV could provide early evidence-base pathology in cigarette smokers prior to development of overt disease. The imperative of this argument is that WBV can be determined with some limitations from routine full blood counts and liver function tests and the laboratory does not require extra equipment to provide this service.^{29,30} Having said that, the equipment and time required for measurement of whole blood viscosity is not expensive and the value of its measurement in a number of common pathologies is becoming apparent.^{26,29}

One respondent expressed that measuring nicotine metabolites is not required to recommend to quit smoking and that telling clients that one cigarette a day will not cause toxicity, as suggested by their metabolite levels, will not help to prevent smoking either.

Against this argument, it is necessary to emphasize evidence-base pathology for early identification and intervention i.e. laboratory test to determine level of subclinical pathology or toxicity. Further, if assessment of cigarette toxicity by counting ‘number of cigars/day’ is inaccurate because there are differences in metabolism due to ethnicity and method of smoking [9], then an alternative method such laboratory evaluation of the metabolic effect e.g. WBV need to be advocated.

Implication for rehabilitation practice

In the words of a Consultant Psychiatrist, the concept of laboratory testing for cigarette toxicity is interesting. In the words of a Consultant Psychiatrist (Personal Communications: 20th February 2014): If it is developed to a point where it becomes possible to grade the degree

of dependence/toxicity based on laboratory assay; this will be handy as it will guide on withdrawal or cessation of nicotine, especially in acute care and psychiatric facilities, where cigarettes smoking is banned. If we can grade; it helps us determine how much of nicotine replacement to give to manage the withdrawal effects, which are troublesome in such settings

Implications for respiratory diseases

Beside the poll responses reported here, it is quite unfortunate to note that laboratory analyses are considered unhelpful in diagnosis of drug-induced pulmonary diseases.²⁴ This is probably due to failure to define the pathophysiology associated with the disease. That is, it is unthoughtful to dismiss the significance of laboratory tests, knowing that bronchoalveolar lavage (BAL) can contribute to the expected clinicopathologic pattern of a given drug-induced lung disease such as identifying eosinophils in a drug-induced eosinophilic pneumonia.²⁴ The implication is that eosinophilic pneumonia is associated with cigarette smoking.³¹⁻³⁴ Indeed, it is very plausible that BAL may be useful for screening early or subclinical respiratory diseases among cigarette smokers.³⁵ Respiratory diseases are also associated with rheological properties of blood, which in turn constitute subclinical vasculopathy with known laboratory biomarkers and cigarette smoke.³⁶⁻³⁹ The obvious implication is that haemorrhheological indices such as whole blood viscosity could be used to screen for early or subclinical respiratory disease before overt symptoms occur.

Laboratory monitoring of therapeutic smoking

There is no argument over the dangers of cigarette smoking, but the smoker's paradox.^{40,41} Cannabis contains δ -9-tetrahydrocannabinol that is associated with alleviation of pain and has been used therapeutically in various cultures for medicinal purposes.

Besides being illegal to possess and use in various countries, cannabis smoking has adverse effects that include increase in heart rate and instability of blood pressure and it also contains similar toxic compounds present in cigarette smoke.⁴²

Especially, there is the call for health practitioners to clearly and convincingly present the data concerning the adverse effects of smoking, as well as the dangers of exposure to environmental smoke, in order to make patients aware that breaking their addiction will not only be beneficial for their own health.⁴³

Further, the smoker's paradox acknowledges the substantial benefits of therapeutic smoking, which has contributed to adoption of therapeutic smoking and development of new drugs.⁴⁰⁻⁴⁵ Therefore, there are justifiable reasons for clinical laboratory testing of smoking toxicity not limited to evidence-based pathology

for early identification and intervention of subclinical pathology in smokers but also laboratory monitoring of therapeutic smoking.

Implication for low-mid income communities

It is known that cigarette smoke constitutes chemicals, containing free radicals and oxidants.⁴⁶ Smoking may therefore enhance oxidative stress possibly through the production of reactive oxygen species radicals in cigarette tar and smoke but also weakening of the anti-oxidant systems.⁴⁷ Further, there is no doubt that passive smoke equally induces oxidative stress in humans.⁴⁸ The issue being brought to the fore is the ignorance or lack of evidence-base pathology in clinical assessment, especially of non-smokers.

That is, passive smokers and non-smoking individuals exposed to domestic and other types of smoke are not correctly classified despite the knowledge that they may have oxidative stress associated with smoking. While this issue is worse for low-mid income countries and even rural communities of high income societies where laboratory services such as blood gas and respiratory function tests are unavailable, the situation can be managed if inexpensive and simple tests such as WBV (using chart method) is adopted; bearing in mind that most laboratories can run full blood counts and liver function tests.

Further implications

Air pollution that comes from different sources is a problem in both high income and low income communities. For instance, fumes from diesel engines can cause chronic obstructive pulmonary disease [49], and this is probably more prevalent in high income communities. In developing countries, smoke from burning of solid fuels indoors (the common practice in low-mid income societies is a serious threat to health of women and children.⁵⁰⁻⁵²

This includes heating, lighting and cooking using firewood and as kerosene. Oxidative damage has been implicated in many diseases and it seems that the mechanism of air pollution-induced health effects involves oxidative stress.⁵³ Increased malondialdehyde level in breath after experimentally exposing adult human subjects to wood smoke is an example of this effect.⁵⁰ Therefore, it is desirable that the dangers of air-pollution smoke are determined when the concept of testing for cigarette smoke toxicity is accepted as important.

CONCLUSION

In regards to 'clinical laboratory testing for cigarette toxicity', two summary points are pertinent. First, it is easy and plausible to rationalise why such test seems unnecessary. However, such a dismissive argument undermines the relevance of the pathology evidence base,

including the concept of diagnosis and management of diseases by laboratory methods. It also means failure to identify the role of medical scientist, in the fight against smoking and its deleterious effects. Secondly, some tests have been identified that could be appropriate to assess cigarette toxicity and this brief survey report puts them into context for useful pathology evidence based practice.

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