International Journal of Research in Medical Sciences
Nwose EU et al. Int J Res Med Sci. 2016 Jun;4(6):2436-2443
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20161827

Short Communication

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

Ezekiel U. Nwose[1*], Phillip T. Bwititi[2], Ross S. Richards[1]

[1]Department of Community Health, Charles Sturt University, Australia
[2]Department of Biomedical Sciences, Charles Sturt University, Australia

Received: 15 April 2016
Accepted: 09 May 2016

***Correspondence:**
Dr. Ezekiel U. Nwose,
E-mail: nwoseeu@gmail.com

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, nornicotine 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
	ALT/AST[19]	Varied
Renal function	GFR[20,21]	Varied
	Proteinuria	Varied
Lipid profile[22]	HDL	Reduced
	Other indices	Varied
Other tests	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 2nd question†						Response to 3rd 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 break-down 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 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 obvert 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 haemorrheological indices such as whole blood viscosity could be used to screen for early or subclinical respiratory disease before obvert 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.

ACKNOWLEDGEMENTS

The authors wish to acknowledge all Bachelor of Medical Laboratory Science 'Clinical Placement of year 2013' students from Charles Darwin University, who participated in polling opinions from health practitioners.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB: General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study. Circulation. 2008;117(6):743-53.
2. Fan H, Bobek LA. Regulation of human MUC7 mucin gene expression by cigarette smoke extract or cigarette smoke and Pseudomonas aeruginosa lipopolysaccharide in human airway epithelial cells and in MUC7 transgenic mice. The open respiratory medicine journal. 2010;4:63-70.
3. Kosmider B, Messier EM, Chu HW, Mason RJ. Human alveolar epithelial cell injury induced by cigarette smoke. PLoS One. 2011;6(12):e26059.
4. Clauss M, Voswinckel R, Rajashekhar G, Sigua NL, Fehrenbach H, et al: Lung endothelial monocyte-activating protein 2 is a mediator of cigarette smoke-induced emphysema in mice. J Clin Invest. 2011;121(6):2470-9.
5. Mossman BT, Lounsbury KM, Reddy SP: Oxidants and signaling by mitogen-activated protein kinases in lung epithelium. American journal of respiratory cell and molecular biology. 2006;34(6):666-9.
6. Jiao ZX, Ao QL, Xiong M: Cigarette smoke extract inhibits the proliferation of alveolar epithelial cells and induces apoptosis. Sheng Li Xue Bao. 2006;58(3):244-54.
7. Gensch E, Gallup M, Sucher A, Li D, Gebremichael A, Lemjabbar H, et al: Tobacco smoke control of mucin production in lung cells requires oxygen radicals AP-1 and JNK. J Biol Chem. 2004;279(37):39085-93.
8. Furer V, Hersch M, Silvetzki N, Breuer GS, Zevin S. Nicotiana glauca (tree tobacco) intoxication-two cases in one family. J Med Toxicol. 2011;7(1):47-51.
9. Benowitz NL, Hukkanen J, Jacob PI. Nicotine Chemistry, Metabolism, Kinetics and Biomarkers. In: Nicotine Psychopharmacology. Edited by Henningfield J, London E, Pogun S, vol. 192: Springer Berlin Heidelberg. 2009;29-60.
10. Moyer TP, Charlson JR, Enger RJ, Dale LC, Ebbert JO, Schroeder DRet al. Simultaneous analysis of nicotine, nicotine metabolites, and tobacco alkaloids in serum or urine by tandem mass spectrometry, with clinically relevant metabolic profiles. Clin Chem. 2002;48(9):1460-71.
11. Yue B, Kushnir MM, Urry FM, Rockwood AL. Quantitation of nicotine, its metabolites, and other related alkaloids in urine, serum, and plasma using LC-MS-MS. Methods in molecular biology (Clifton, NJ). 2010,603:389-98.
12. Tricker AR: Biomarkers derived from nicotine and its metabolites: a review. Beitrage zur Tabakforschung International/Contributions to Tobacoo Research. 2006,22(3):147-75.
13. Warren FC, Abel G, Lyratzopoulos G, Elliott MN, Richards S, Barry HE, et al. Characteristics of service users and provider organisations associated with experience of out of hours general practitioner care in England: population based cross sectional postal questionnaire survey. BMJ 2015, 350:h2040.
14. Galea G, Davidson RJ. Haematological and haemorheological changes associated with cigarette smoking. J Clin Pathol. 1985,38(9):978-84.
15. Salamzadeh J. The hematologic effects of cigarette smoking in healthy men volunteers. Iranian Journal of Pharmaceutical Research. 2004, 3(Suppl 2):41.
16. Passamonti F: How I treat polycythemia vera. Blood 2012;120(2):275-84.
17. D'Souza SW, Black PM, Williams N, Jennison RF: Effect of smoking during pregnancy upon the haematological values of cord blood. British journal of obstetrics and gynaecology. 1978;85(7):495-9.
18. Wannamethee SG, Shaper AG. Cigarette smoking and serum liver enzymes: the role of alcohol and inflammation. Annals of Clinical Biochemistry. 2010;47(4):321-6.
19. Whitehead TP, Robinson D, Allaway SL: The effects of cigarette smoking and alcohol consumption on serum liver enzyme activities: a dose-related study in men. Ann Clin Biochem. 1996;33(Pt 6):530-5.
20. Garcia-Esquinas E, Loeffler LF, Weaver VM, Fadrowski JJ, Navas-Acien. A: Kidney function and tobacco smoke exposure in US adolescents. Pediatrics. 2013;131(5):e1415-23.
21. Noborisaka Y, Ishizaki M, Nakata M, Yamada Y, Honda R, Yokoyama H, et al. Cigarette smoking, proteinuria, and renal function in middle-aged Japanese men from an occupational population. Environmental health and preventive medicine 2012;17(2):147-56.
22. Muniyappa R, Sable S, Ouwerkerk R, Mari A, Gharib AM, Walter M et al: Metabolic effects of chronic cannabis smoking. Diabetes Care. 2013;36(8):2415-22.
23. Erdemir EO, Bergstrom J. Relationship between smoking and folic acid, vitamin B12 and some haematological variables in patients with chronic

periodontal disease. J Clin Periodontol. 2006;33(12):878-84.
24. Byrd RP: Drug-induced pulmonary toxicity. Medscape 2015.
25. Jang ES, Jeong SH, Hwang SH, Kim HY, Ahn SY, Lee J, et al: Effects of coffee, smoking, and alcohol on liver function tests: a comprehensive cross-sectional study. BMC gastroenterology. 2012;12:145.
26. Gyawali P, Richards RS, Nwose EU, Bwititi PT. Whole-blood viscosity and metabolic syndrome. Clinical Lipidology. 2012;7(6):709-19.
27. Gyawali P, Richards RS, Bwititi PT, Nwose EU: Association of abnormal erythrocyte morphology with oxidative stress and inflammation in metabolic syndrome. Blood cells, molecules & diseases 2015.
28. Kwiatkowski TC, Hanley EN, Jr., Ramp WK: Cigarette smoking and its orthopedic consequences. American journal of orthopedics (Belle Mead, NJ) 1996;25(9):590-7.
29. Nwose EU: Whole blood viscosity assessment issues I: Extrapolation chart and reference values. North Am J Med Sci. 2010;2(4):165-9.
30. Nwose EU, Butkowski EG. Algorithm for whole blood viscosity: Implication for antiplatelet bleeding risk assessment. Austr J Med Sc. 2013;34(2):50-5.
31. Shiota Y, Kawai T, Matsumoto H, Hiyama J, Tokuda Y, Marukawa M, et al. Acute eosinophilic pneumonia following cigarette smoking. Internal medicine (Tokyo, Japan). 2000;39(10):830-3.
32. Shintani H, Fujimura M, Yasui M, Ueda K, Kameda S, Noto M, et al. Acute eosinophilic pneumonia caused by cigarette smoking. Internal medicine (Tokyo, Japan). 2000;39(1):66-8.
33. Shorr AF, Scoville SL, Cersovsky SB, Shanks GD, Ockenhouse CF, Smoak BL, et al. Acute eosinophilic pneumonia among US Military personnel deployed in or near Iraq. Jama. 2004;292(24):2997-3005.
34. Natarajan A, Shah P, Mirrakhimov AE, Hussain N. Eosinophilic pneumonia associated with concomitant cigarette and marijuana smoking. BMJ case reports. 2013, 2013.
35. Caminati A, Cavazza A, Sverzellati N, Harari S. An integrated approach in the diagnosis of smoking-related interstitial lung diseases. European respiratory review: an official journal of the European Respiratory Society. 2012;21(125):207-17.
36. Tazbirek M, Slowinska L, Kawalski M, Pierzchala W. The rheological properties of blood and the risk of cardiovascular disease in patients with obstructive sleep apnea syndrome (OSAS). Folia histochemica et cytobiologica / Polish Academy of Sciences, Polish Histochemical and Cytochemical Society. 2011;49(2):206-10.
37. Liak C, Fitzpatrick M. Coagulability in obstructive sleep apnea. Canadian respiratory journal : journal of the Canadian Thoracic Society. 2011;18(6):338-48.
38. Yarnell JW, Sweetnam PM, Rogers S, Elwood PC, Bainton D, Baker IA, et al. Some long term effects of smoking on the haemostatic system: a report from the Caerphilly and Speedwell Collaborative Surveys. J Clin Pathol. 1987;40(8):909-13.
39. Jefferis BJ, Lowe GD, Welsh P, Rumley A, Lawlor DA, Ebrahim S, et al: Secondhand smoke (SHS) exposure is associated with circulating markers of inflammation and endothelial function in adult men and women. Atherosclerosis. 2010;208(2):550-6.
40. Aune E, Roislien J, Mathisen M, Thelle DS, Otterstad JE. The "smoker's paradox" in patients with acute coronary syndrome: a systematic review. BMC medicine. 2011;9:97.
41. Rahn EJ, Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics. 2009;6(4):713-37.
42. Leung L. Cannabis and its derivatives: review of medical use. Journal of the American Board of Family Medicine : JABFM. 2011;24(4):452-62.
43. Sikorska-Jaroszynska MH, Mielnik-Blaszczak M, Krawczyk D, Nasilowska-Barud A, Blaszczak J. Passive smoking as an environmental health risk factor. Annals of agricultural and environmental medicine : AAEM. 2012;19(3):547-50.
44. Chaplan SR, Eckert WA, Carruthers NI. Drug Discovery and Development for Pain. In: Translational Pain Research: From Mouse to Man. Edited by Kruger L, Light AR. Boca Raton, FL: CRC Press; 2010.
45. Quik M, Perez XA, Bordia T: Nicotine as a potential neuroprotective agent for Parkinson's disease. Movement disorders: official journal of the Movement Disorder Society. 2012;27(8):947-57.
46. Tavilani H, Nadi E, Karimi J, Goodarzi MT. Oxidative stress in COPD patients, smokers and non-smokers. Respir Care. 2012;57(12):2090-94.
47. Burlakova EB, Zhizhina GP, Gurevich SM, Fatkullina LD, Kozachenko AI, Nagler LG, et al. Biomarkers of oxidative stress and smoking in cancer patients. Journal of cancer research and therapeutics. 2010;6(1):47-53.
48. Kato T, Inoue T, Morooka T, Yoshimoto N, Node K: Short-term passive smoking causes endothelial dysfunction via oxidative stress in nonsmokers. Can J Physiol Pharmacol. 2006;84(5):523-9.
49. Hart JE, Eisen EA, Laden F. Occupational diesel exhaust exposure as a risk factor for chronic obstructive pulmonary disease. Current opinion in pulmonary medicine. 2012;18(2):151-4.
50. Barregard L, Sallsten G, Andersson L, Almstrand AC, Gustafson P, Andersson M, et al. Experimental exposure to wood smoke: effects on airway inflammation and oxidative stress. Occup Environ Med. 2008;65(5):319-24.
51. Moulton PV, Yang W. Air pollution, oxidative stress, and Alzheimer's disease. Journal of environmental and public health. 2012;2012:472751.
52. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease

and risk factors, 2001: systematic analysis of population health data. Lancet. 2006;367(9524):1747-57.
53. Lodovici M, Bigagli E. Oxidative stress and air pollution exposure. Journal of toxicology. 2011;2011:487074.

Cite this article as: Nwose EU, Bwititi PT, Richards RS. Clinical laboratory testing for smoking toxicity: implications for early identification of respiratory diseases. Int J Res Med Sci 2016;4:2436-43.