J Med Sci, Volume 49, No. 1, 2017 January: 31-37

Smoking cessation reduces ratio of total cholesterol/high density lipoprotein (HDL) cholesterol levels on adult people in Yogyakarta Special Region

Arta Farmawati[1*], Ratika Marchelaona[2], Dina Septari Anindyah[3]
[1]Department of Biochemistry, [2]Postgaduate Program in Basic Medical and Biomedical Sciences, [3]Department of Health Nutrition, Faculty of Medicine, Univesitas Gadjah Mada, Yogyakarta, Indonesia

DOI: http://dx.doi.org/10.19106/JMedSci004901201705

ABSTRACT

Cigarette smoking is a major cause of cardiovascular disease due to elevation of free radical substances as well impairment in lipid metabolism. Smoking cesation has been linked with reduced risk of mortality. However, data regarding cardiovascular disease (CVD) risk factor in former smoker is limited. The aim of the study was to evaluate the CVD risk factor among smoker, non-smoker and former smoker in Yogyakarta Special Region, Indonesia. A cross-sectional design from 86 apparently healthy male, aged between 25-50 years old was performed for this study. From total subjects, 45 subjects are smokers, 26 are non-smokers and 15 are former smokers. Body weight, height, and blood pressure were also measured from the subjects. Blood was drawn for assessment of total cholesterol (TC), triglyceride, low density lipoprotein (LDL), high density lipoprotein (HDL) and C-reactive protein (CRP) concentrations. We found significant difference in the level of HDL, cardiovascular risk index (LDL/HDL ratio), atherogenic index (TC/HDL ratio) and also in systolic blood pressure among groups ($p<0.05$). Smoking person had significantly low HDL level with high CVD risk index and atherogenic index ($p<0.05$). The CVD risk index was not different between former smoker and smoker groups. Serum CRP level was not different among the groups. In conclusion, smoking is associated with increased risk of CVD. Smoking cessation slightly decrease the CVD risk.

ABSTRAK

Merokok merupakan penyebab utama penyakit kardiovaskuler akibat kenaikan radikal bebas dan gangguan metabolisme lipid. Berhenti merokok dihubungkan dengan menurunnya risiko kemation. Namun demikian, data mengenai faktor risiko penyakit kardiovaskuler mantan perokok sangat terbatas. Penelitian ini bertujuan mengkaji faktor risiko penyakit kardiovaskuler diantara perokok, bukan perokok dan mantan perokok di Daerah Istimewa Yogyakarta, Indonesia. Penelitian dengan rancangan potong lintang terhadap 86 lelaki sehat secara klinis, berumur 25-50 tahun dilakukan dalam penelitian ini. Dari total 86 subjek, 45 merupakan perokok, 26 bukan perokok dan 15 mantan perokok. Berat badan, tinggi badan dan tekanan darah juga dimonitor dalam penelitian. Sampel darah diambil untuk pemeriksaan kadar kolesterol total, trigliserida, *low density lipoprotein* (LDL), *high density lipoprotein* (HDL) and protein C-reaktif (CRP). Perbedaan nyata ditemukan dalam

Corresponding author: a.farmawati@ugm.ac.id

kadar HDL, indeks risiko kardiovaskuler (rasio LDL/HDL), indeks atherogenic (rasio TC/HDL) dan juga tekanan darah diantara kelompok subjek ($p<0,05$). Perokok mempunyai kadar HDL lebih rendah secara nyata dengan indeks risiko kardiovaskuler tinggi dan indeks atherogenic tinggi ($p<0,05$). Indeks risiko menderita penyakit kardiovaskuler antara mantan perokok dan perokok tidak berbeda nyata. Kadar CRP serum tidak berbeda nyata antar keompok ($p>0,05$). Kesimpulan, merokok berhubungan dengan meningkatna risiko menderita penyakit kardiovakuler. Berhenti merokok dapat sedikit mengurangi risiko penyakit kardiovaskuler.

Keywords: Cigarette smoking - cardiovascular disease – C-reactive protein - lipid profile - atherogenic index

INTRODUCTION

Cigarette smoking is the most major significance cause of death worldwide. It was estimated that 20% of death of adult men and 5% of death of adult women were attributed to the use of tobaco smoking. In addition, approximately 450 million adults aged between 30 and 69 years old were killed in the last 5 decades.[1,2] The majority of these death occur in the economically developing countries where the regulation and taxes regarding cigarette smoking is loosen.[1] Moreover, smoking causes over US$ 500 billion in economic loss annually.[3]

Indonesia is one of the smoker high prevalence countries in Southeast Asia with prevalence of 35.7%.[4,5] Early exposure to cigarette smoking due to environmental factors are associated with the high prevalence of cigarette smoking in Indonesia.[6] If action is not taken, more adult people will be killed by smoking-related disease particularly lung cancer[7] and cardiovascular disease (CVD).[8] High exposure of free radicals derived from cigarette smoke (the tar and the gas phase) has been proposed as the mechanism between smoking and CVD development.[9] High free radical derived from cigarette smoke activates intracellular signaling cascades that promotes chronic immune cell recruitment and inflammation through activation of several inflammatory gene, e.g. interleukin (IL)-8 and tumor necrosis factor-α (TNF-α).[10-12]

C-reactive protein (CRP) is an acute phase protein, which is synthesized in response to systemic inflammation. It is associated with the progression of CVD event[13] as well in malignancies development.[14,15] Increased in CRP level as a result of tissue injury has been observed in smoking person even after cessation of cigarette smoking, indicating the high risk of CVD in former smoker.[16] Although CRP is not the only sole predictor of CVD event in smoker, however, CRP level in the blood is positively correlated with reactive oxygen metabolites.[17,18] The high reactive oxygen metabolites in the blood may accelerate the progression of plaque formation through the formation of oxidized-LDL.[19] In addition, low HDL level has also been observed in cigarette smoker, which will aggravate the formation of oxidized-LDL.[20] Cessation of cigarette smoking has been associated with increased size and particle of HDL.[21] However, data regarding the CVD risk of former smoker is limited. This study was performed to evaluate the CVD risk factor in smoker, non-smoker and former smoker in Yogyakarta Special Region, Indonesia.

MATERIALS AND METHODS

Study design and subjects

A cross sectional study was performed between May-June 2015 using multistage cluster random sampling throughout 23 districts in Yogyakarta Special Region. Data were collected based on the inclusion criteria as follow: male, aged between 25 to 50 years old, did not diagnosed with chronic disease, reside in the Yogyakarta Special Region for over 5 years, and willing to be a subject proofed by filling the informed consent form. Eighty six (86) subjects that comprised by 45 current smokers, 15 former smokers and 26 non-smokers were sucessfully recruited in this study. Former smoker was defined as person who quit smoking for more than 1 year. Subjects were subjected to 8 hour fast prior to blood drawn. The study protocol has been approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia (No. KE/FK/665/EC/2015).

Biochemical analysis

After signed an informed consent, subjects were subjected to an 8 hours fasting. Approximately, 8 mL of blood sample was drawn and centrifuged briefly to obtain serum. Serum was then stored in -20° C until analysis or analyzed directly for total cholesterol, triglyceride, LDL, HDL and serum CRP levels. Total cholesterol and triglycerides were analysized using enzymatic colorimetris method using cholesterol test kit (cholesterol FS, Diasys, Germany) and triglyceride test kit (triglyceride FS, Dyasis, Germany) according to manufacturer protocol. LDL and HDL were precipitated first prior to the analysis using HDL and LDL cholesterol test kit (Dyasis, Germany). Serum CRP level was analyzed using human CRP ELISA kit (Thermo Fisher Scientific, USA) according to manufacturer protocol. Body weight was measured using digital scale (Camry) in minimal clothes. Height and blood pressure were measured using standardized procedure. Body mass index (BMI) was calculated based on body weight and body height. All measurement were performed in triplicates.

Statistical analysis

Data were presented as mean ± standard deviation (SD) and analyzed using one way analysis of variance (ANOVA) followed by student t-test. All data analysis were performed in SPSS version 20 (IBM, USA). A p value < 0.05 was considered significant.

RESULTS

No significantly different between age, body weight, height, BMI and distolic blood pressure among smoker, former smoker and non-smoker were observed in this study (TABLE 1). It was indicated that subjects had similar characteristic between group although the systolic blood pressure was found to be significantly different among groups ($p<0.05$).

TABLE 1. Baseline characteristics of subjects

Variables	Status (mean ± SD)			p
	Smoker	Former smoker	Non-smoker	
Age (year)	39.33±5.70	42.07±6.08	40.94±6.61	0.262
Body Weight (kg)	66.54±10.93	68.77±13.12	68.81±13.46	0.691
Height (cm)	164.62±6.52	161.33±4.79	165.30±5.22	0.102
BMI (kg/m^2)	24.49±3.40	26.52±5.44	25.06±4.00	0.243
Systole	114.00±15.51	122.67±19.89	122.69±13.73	0.045
Diastole	77.56±11.85	77.67±12.94	82.31±10.51	0.232

No significantly different in total cholesterol, triglyceride, and LDL between smoker, former smoker and non-smoker were observed in this study (TABLE 2). However, the total cholesterol and triglyceride of smoker tended to be higher than former smoker and non smoker ($p>0.05$). In contrast, the HDLlevels were found to be significantly different among group with the lowest level was observed in smoker group ($p<0.05$). Furthermore, LDL/HDL and total cholesterol/HDL ratio in smoker group were significantly higher than in former smoker and non smoker ($p<0.05$). The serum CRP level of non-smoker was lower than that formal smoker and smoker. However, it was not significantly different ($p> 0.05$).

TABLE 2. Lipid profile and CRP level in smoker, former smoker and non-smoker groups

Variables	Status (mean ± SD)			p
	Smoker	Former smoker	Non-smoker	
Total cholesterol (mg/dL)	205.91±37.60	198.80±30.86	189.92±36.11	0.203
Triglycerides (mg/dL)	208.04±159.01	138.40±70.96	150.73±98.15	0.094
LDL (mg/dL)	131.56±34.97	135.33±29.15	120.88±32.40	0.313
HDL (mg/dL)	38.82±7.29	43.13±6.93	42.88±7.24	0.033
LDL/HDL ratio	3.44±0.82^{ab}	3.20±0.78^{bc}	2.87±0.79^{c}	0.019
TC/HDL ratio	5.45±1.18^{a}	4.69±0.92^{b}	4.52±0.99^{b}	0.002
CRP (mg/L)	3.25±5.15	2.44±3.55	1.79±1.27	0.965

$^{a,b,c:}$ different notation indicated significantly different ($p<0.05$)

DISCUSSION

Smoking is the most significance cause of CVD in the world. Smoking has been associated with 3 to 5.6 times risk of acute myocardial infarctions than non-smoker in similar age.[22,23] Smoking cesation has been associated with 36% reduction in crude relative risk (RR) of mortality as well 32% reduction in non-fatal myocardial infarction.[24,25] The reduction in CVD mortality by smoking cessation is caused by improvement in lipid profile (elevated level of HDL with reduced level of LDL).[21,26,27] as well in reduced systemic inflammation marker IL-6.[28]

In our study, no significantly different in serum CRP level between smoker, former smoker and non-smoker due to the high biological variability (high standard

deviation) was observed. This result was also observed in other studies.[16,28,29] However, although statistically the serum CRP level was not significantly different, it tended to be higher in smoker compared to former smoker and non-smoker. It was indicated smoker is still in higher inflammation state. Our study observed approximately 25% lower in serum CRP level in former smoker indicating better inflammation status when cigarette smoking was ceased.

We observed a significant higher level of HDL-cholesterol in former smoker and non-smoker compared with smoker, which, again, indicated the beneficial effect of smoking cessation in ameliorating CVD risk through elevation of HDL level. We did not find any difference in the level of total cholesterol, triglyceride, and LDL level among the groups that was similar with previous studies.[21,30] We also observed a reduction in CVD risk index and total/HDL cholesterol ratio or Castelli index in former smoker compared with smoker although the level of LDL/HDL ratio was not significantly different compared to that the smoker group. Total/high-density lipoprotein (HDL) cholesterol and LDL/HDL cholesterol ratios are risk indicators with greater predictive value than LDL or HDL alone.[31,32] A ratio LDL/HDL of 2.3 to 2.5 can predict the CVD risk factors in the population.[32,33]

CONCLUSION

In conclusion, smoking cessation is associated with the reduce of total cholesterol/ HDL cholesterol ratio on adult people indicating the reduce of CVD risk.

ACKNOWLEDGEMENTS

This study is supported in part by funds provided through *Dana Masyarakat* (Community Funding), Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia.

REFERENCES

1. Jha P, Mac Lennan M, Chaloupka FJ, Yurekli A, Ramasundarahettige C, Palipudi K, *et al.* Global hazards of tobacco and the benefits of smoking cessation and tobacco taxes. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, editors. Disease control priorities: cancer. Washington (DC): The International Bank for Reconstruction and Development / The World Bank, 2015. doi:10.1596/978-1-4648-0349-9_ch10.
2. Jha P. Avoidable global cancer deaths and total deaths from smoking. Nat Rev Cancer 2009; 9:655–64. doi:10.1038/nrc2703.
3. Ekpu VU, Brown AK. The economic impact of smoking and of reducing smoking prevalence: review of evidence. Tob Use Insights 2015;8:1–35. doi:10.4137/TUI.S15628.
4. Tee GH, Aris T, Rarick J, Irimie S. Social determinants of health and tobacco use in five low and middle-income countries - results from the Global Adult Tobacco Survey (GATS), 2011 - 2012. Asian Pac J Cancer Prev 2016;17:1269–76.
5. Palipudi K, Mbulo L, Kosen S, Tjandra A, Kadarmanto, Qureshi F, *et al.* A cross sectional study of kretek smoking in indonesia as a major risk to public health. Asian Pac J Cancer Prev 2015;16:6883–8.
6. Sukamdi, Wattie AM. Tobacco use and exposure among children in migrant and non-migrant households in Java, Indonesia. Asian Pac Migr J 2013;22:447–64.
7. Islami F, Torre LA, Jemal A. Global trends of lung cancer mortality and smoking prevalence. Transl Lung Cancer Res 2015;4:327–38. doi:10.3978/j.issn.2218-6751.2015.08.04.

8. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, *et al.* Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. Eur Heart J 2008; 29:932–40. doi:10.1093/eurheartj/ehn018.
9. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol 2004; 43:1731–7.
10. Lee J, Taneja V, Vassallo R. Cigarette smoking and inflammation: cellular and molecular mechanisms. J Dent Res 2012; 91:142–9. doi:10.1177/0022034511421200.
11. Churg A, Dai J, Tai H, Xie C, Wright JL. Tumor necrosis factor-alpha is central to acute cigarette smoke-induced inflammation and connective tissue breakdown. Am J Respir Crit Care Med 2002;166:849–54. doi:10.1164/rccm.200202-097OC.
12. Chung KF. Inflammatory mediators in chronic obstructive pulmonary disease. Curr Drug Targets Inflamm Allergy 2005;4:619–25.
13. Bisoendial RJ, Boekholdt SM, Vergeer M, Stroes ESG, Kastelein JJP. C-reactive protein is a mediator of cardiovascular disease. Eur Heart J 2010;31:2087–91. doi:10.1093/eurheartj/ehq238.
14. Allin KH, Nordestgaard BG. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. Crit Rev Clin Lab Sci 2011;48:155–70. doi:10.3109/10408363.2011.599831.
15. Heikkila K, Ebrahim S, Lawlor DA. A systematic review of the association between circulating concentrations of C reactive protein and cancer. J Epidemiol Community Health 2007;61:824–33. doi:10.1136/jech.2006.051292.
16. Hastie CE, Haw S, Pell JP. Impact of smoking cessation and lifetime exposure on C-reactive protein. Nicotine Tob Res 2008;10:637–42. doi:10.1080/14622200801978722.
17. Kotani K, Sakane N. C-reactive protein and reactive oxygen metabolites in subjects with metabolic syndrome. J Int Med Res 2012;40:1074–81.
18. Harris MT, Davis WW, Le N-A, Eggleston B, Austin GE, Moussa M, *et al.* Free oxygen radicals in whole blood correlate strongly with high-sensitivity C-reactive protein. J Clin Lipidol 2007;1:593–8. doi:10.1016/j.jacl.2007.10.008.
19. Li D, Mehta JL. Oxidized LDL, a critical factor in atherogenesis. Cardiovasc Res 2005;68:353–4. doi:10.1016/j.cardiores.2005.09.009.
20. MERTENS ANN, HOLVOET P. Oxidized LDL and HDL: antagonists in atherothrombosis. FASEB J 2001;15 :2073–84. doi:10.1096/fj.01-0273rev .
21. Gepner AD, Piper ME, Johnson HM, Fiore MC, Baker TB, Stein JH. Effects of Smoking and smoking cessation on lipids and lipoproteins: outcomes from a randomized clinical Trial. Am Heart J 2011;161:145–51. doi:10.1016/j.ahj.2010.09.023.
22. Burns DM. Epidemiology of smoking-induced cardiovascular disease. Prog Cardiovasc Dis 2003;46:11–29.
23. Benowitz NL. Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. Prog Cardiovasc Dis 2003;46:91–111.
24. Critchley J, Capewell S. Smoking cessation for the secondary prevention of coronary heart disease. Cochrane Database Syst Rev 2004:CD003041. doi:10.1002/14651858.CD003041.pub2.
25. Critchley JA, Capewell S. WITHDRAWN: Smoking cessation for the secondary prevention of coronary heart disease. Cochrane Database Syst Rev 2012;2:CD003041. doi:10.1002/14651858.CD003041.pub3.
26. Eliasson B, Hjalmarson A, Kruse E, Landfeldt B, Westin A. Effect of smoking

reduction and cessation on cardiovascular risk factors. Nicotine Tob Res 2001;3:249–55. doi:10.1080/14622200110050510.

27. Maeda K, Noguchi Y, Fukui T. The effects of cessation from cigarette smoking on the lipid and lipoprotein profiles: a meta-analysis. Prev Med (Baltim) 2003;37:283–90.
28. Aldaham S, Foote JA, Chow H-HS, Hakim IA. Smoking status effect on inflammatory markers in a randomized trial of current and former heavy smokers. Int J Inflam 2015;2015:439396. doi:10.1155/2015/439396.
29. Asthana A, Johnson HM, Piper ME, Fiore MC, Baker TB, Stein JH. Effects of smoking intensity and cessation on inflammatory markers in a large cohort of active smokers. Am Heart J 2010;160:458–63. doi:10.1016/j.ahj.2010.06.006.
30. Gossett LK, Johnson HM, Piper ME, Fiore MC, Baker TB, Stein JH. Smoking intensity and lipoprotein abnormalities in active smokers. J Clin Lipidol 2009;3:372–8. doi:10.1016/j.jacl.2009.10.008.
31. Millán J, Pintó X, Muñoz A, Zúñiga M, Rubiés-Prat J, Pallardo LF, *et al.* Lipoprotein ratios: Physiological significance and clinical usefulness in cardiovascular prevention. Vasc Health Risk Manag 2009;5:757–65.
32. Enomoto M, Adachi H, Hirai Y, Fukami A, Satoh A, Otsuka M, *et al.* LDL-C/HDL-C ratio predicts carotid intima-media thickness progression better than HDL-C or LDL-C alone. J Lipids 2011;2011:549137. doi:10.1155/2011/549137.
33. Chen Q-J, Lai H-M, Chen B-D, Li X-M, Zhai H, He C-H, *et al.* Appropriate LDL-C-to-HDL-C ratio cutoffs for categorization of cardiovascular disease risk factors among Uygur adults in Xinjiang, China. Int J Environ Res Public Health 2016;13:235. doi:10.3390/ijerph13020235.