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Correlation of Lipid Parameters and Markers of Insulin Resistance: Does Smoking Make a Difference?

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Summary

Insulin resistance associated with dyslipidemia enhances cardiovascular risk. Several atherogenic indexes have been suggested to give more precise information about the risk. The aim of our study was to estimate, which atherogenic index correlates better with parameters of insulin resistance. Furthermore, we compared the parameters of lipid metabolism and insulin resistance between smokers and non-smokers. In our cross-sectional study we enrolled 729 patients with dyslipidemia which were divided into two groups – non-smokers (586) and smokers (143). We measured lipid profile, parameters of insulin resistance (fasting glycemia, insulin, HOMA-IR, C-peptide, proinsulin) and calculated atherogenic indexes – atherogenic index of plasma (log (TAG/HDL-C), AIP), ApoB/ApoA1 index and nonHDL-C. AIP was found out to show stronger correlations with parameters of insulin resistance ($p<0.001$, correlation coefficients ranging between 0.457 and 0.243) than other indexes (ApoB/ApoA1 or nonHDL cholesterol). AIP correlated with parameters of insulin resistance both in smokers and non-smokers, but after adjustment (for age, body mass index, waist circumference) persisting only in non-smokers. Smokers had a wider waist circumference and a proatherogenic lipid profile. Smoking increases the risk of developing metabolic syndrome. AIP can be used in daily praxis for predicting insulin resistance in patients with dyslipidemia, predominantly in non-smokers.

Key words

Insulin resistance • Metabolic syndrome • Lipid metabolism • Smoking habit • Atherogenic index

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Introduction

The incidence of metabolic syndrome is increasing worldwide. Although insulin resistance is crucial to the pathogenesis of this syndrome, the associated atherogenic lipoprotein phenotype considerably enhances the risk of cardiovascular complications. Several so called atherogenic indexes have been suggested to give more precise information about the present cardiovascular risk. These indexes are calculated from measured values of plasma lipids. One of the recommended indexes is the atherogenic index of plasma (AIP). AIP is calculated as a log (TAG/HDL-C) with triacylglycerols (TAG) and high density lipoprotein cholesterol (HDL-C) expressed in molar concentrations and was proposed by Dobiasova *et al.* (2001) and Frohlich *et al.* (2003). The association of TAG and HDL-C in this ratio reflects the balance between risk and protective lipoprotein forces. Both TAG and HDL-C are widely measured and available. Low HDL-C and high TAG concentrations induce both an increase in small HDL particle and an increase in small, dense low density lipoprotein cholesterol (LDL-C) particles (Dobiasova 2004). AIP has been found to be an important tool for

analyzing the results of clinical trials, assessing not only cardiovascular risk, but also changes in the lipoprotein profile during therapy of diabetes (Dobiasova 2004, Tan *et al.* 2004, Essiarab *et al.* 2014, Zhu *et al.* 2014).

Comparing LDL-C and non HDL-C, non HDL-C has been shown to be a better marker of risk both in primary and secondary prevention studies (Virani 2011). In an analysis of data combined form 68 studies, non HDL-C was the best predictor among cholesterol measures, both for cardiovascular events and for strokes (Di Angelantonio *et al.* 2009). Another effective predictor of coronary heart disease risk is apolipoprotein B/ apolipoprotein A1 index (ApoB/ApoA1), especially in overweight and obesity (Lu *et al.* 2011). It is associated with early atherosclerosis (Panayiotou *et al.* 2008) and estimates the balance between plasma proatherogenic and antiatherogenic lipoproteins (Walldius *et al.* 2004).

In our cross sectional study, we compared AIP with other above mentioned atherogenic indexes (ApoB/ApoA1 and non HDL-C) in order to find out, which atherogenic index correlates better with parameters of insulin resistance. Furthermore, we split up our study group into smokers and non-smokers, and compared the parameters of lipid metabolism and insulin resistance between these two groups.

The reason for this sorting was the fact, that smoking may influence parameters of both lipid and glucose metabolism by reducing insulin sensitivity and inducing insulin resistance (e.g. Targher *et al.* 1997, Lathi-Koski *et al.* 2002). Smoking contributes to advancement of metabolic syndrome in several ways: it stimulates sympatic nervous activity and enhances energetic expenditure. *Via* increasing of lipomobilisation, it can increase the supply of fatty acids to liver, skeletal muscles and stimulate growth of visceral fatty tissue (Kim *et al.* 2012). This situation is worsened by negative influence of smoking on 11beta-hydroxysteroid dehydrogenase (Al Bakir *et al.* 2008) that enables inactivation of cortisol on cortisone. This leads to hypercortisolism which accentuates negative impact of increasing visceral fat.

Methods

729 patients (350 men and 379 women) of the Lipid Center at the University Hospital Olomouc who came for their first visit because of hyperlipidemia (total cholesterol ≥5 mmol/l and/or TAG ≥1.7 mmol/l) between January 2005 and January 2013 were included in the study. Detailed medical history was obtained and physical examination performed. All subjects were tested for secondary hyperlipidemia, particularly diabetes mellitus, hypothyroidism, hepatic or renal failure. Exclusion criteria were as follows: lipid lowering therapy in previous 6 weeks, the presence of diabetes mellitus or other secondary hyperlipidemias, acute infection or trauma, acute cardiovascular event in the last 3 months, and heart failure NYHA III and IV. Patients were asked about their smoking secession and divided into smokers and non-smokers, whereas an ex-smoker was recorded as a non-smoker when he quit at a young age or had not smoked for a substantial time period (Marston *et al*. 2014).

The study was reviewed and approved by the institutional Ethics Committee of the Medical Faculty and University Hospital Olomouc and the informed consent was obtained from all subjects.

Venous blood samples were drawn after a 12 h of overnight fast. Total cholesterol (TC) and TAG concentrations were measured by standard enzymatic methods (CHOD-PAP and GPO-PAP; Roche Diagnostics, Basel, Switzerland). HDL-C was measured by a direct method (both from Roche Diagnostics, Basel, Switzerland). All assays were performed in a COBAS c8000 biochemical analyzer from Roche. LDL-C levels were calculated according to Friewald formula. AIP was calculated as a log (TAG/HDL-C) (Frohlich *et al.* 2003) and non HDL-C as TC – HDL-C. Concentration of ApoB and apolipoprotein A1 (ApoA1) was determined immunoturbidimetrically on Modular SWA analyzer (TinaQuant Apo A1, TinaQuant Apo B kits, all Roche, Basel, Switzerland). Glycemia was determined using the enzyme based Glucose GOD-PAP kit. Insulin was determined using Insuline kit (Immunotech, Marseille, France) with specific antibodies by IRMA method. The result obtained were then used for calculation of HOMA-IR (homeostatis model assessment: fasting glycemia*fasting insulin/22.5) (Matthews *et al.* 1985). C-peptide and proinsulin were determined using the commercially available kit – C-peptide (Immunotech, Marseille, France), Proinsulin (DRG Instruments GmbH, Marburg, Germany) using specific anti-bodies by IRMA method (for C-peptide) and RIA method (for proinsulin). Parameters with normal distribution (normality tested with Kolmogorov-Smirnov test) were compared with Student´s t-test (patients´ age) and expressed as mean ± SD. Parameters with skewed distribution (BMI, waist circumference, total cholesterol, TAG, HDL-C, LDL-C, ApoB, glycemia, insulin, HOMA-IR, C-peptide, proinsulin) were analyzed with Mann-Whitney U-tests and

expressed as median (1^{st}-3^{rd} quartile). Spearman´s correlation and partial correlation coefficient was used in order to determine the association among parameters of insulin resistance and lipid metabolism and also for testing difference between correlation coefficients. Stepwise Forward LR model was used for logistic regression.

Results

We divided our study group into 586 non-smokers and 143 smokers. The mean age of smokers (44.3±13.5 years) and non-smokers (45.6±15.5 years) did not significantly differ between groups. Both groups did not differ in body mass index (BMI), but smokers had a wider waist circumference, showing higher amount of visceral fat in smokers. Overall smokers had a proatherogenic lipid profile (higher TC, TAG, AIP, nonHDL-C, ApoB and lower HDL-C, ApoA1) and also statistically significant worse parameters of insulin resistance (fasting glycemia, insulin, HOMA-IR, C-peptide, proinsulin). Data are presented in Table 1.

AIP correlated better with all parameters of insulin resistance in comparison with ApoB/ApoA1 index and nonHDL-C both in the whole group and also both in smokers and non-smokers, but after adjustment (for age, BMI, waist circumference, sex) persisting only in non-smokers, as shown in Table 2. Testing difference between atherogenic indexes (AIP versus non HDL and AIP versus ApoB/ApoA1 showed significant differences between them ($p<0.003$).

According to logistic regression for predicting higher levels of glucose, age (OR=1.40, $p<0.0005$, 95 % confidence interval for OR 1.17-1.66), level of TAG (OR=1.13, $p<0.005$, 95 % confidence interval for OR 1.04-1.23) and waist circumference (OR=1.67, $p<0.0001$, 95 % confidence interval for OR 1.38-2.02) have been shown as the most relevant predictors, where OR is counted for change in age of 10 years, in TAG of 1 mmol/l and 10 cm in waist circumference. TAG (OR=1.32, $p<0.005$, 95 % confidence interval for OR 1.09-1.61) and waist circumference (OR=1.52, $p<0.0001$, 95 % confidence interval for OR 1.26-1.82) are the most relevant predictors of insulin level. Waist circumference showed in both cases most significant correlations.

Table 1. Parameters of lipid metabolism and insulin resistance in smokers and non-smokers.

	Whole group	**Non-smokers**	**Smokers**
BMI (kg/m^2)	25.5 (23-28.6)	25.4 (23-28.3)	26.3 (23.1-29.4)
Age (years)	45.3 ± 15.2	45.6 ± 15.5	44.3 ± 13.5
Sex (female/male)	379 female	319 female	60 female
	350 male	257 male	83 male
Waist circumference (cm)	87 (77-97)	86 (76-95)	90 (79-99) +
Total cholesterol (mmol/l)	6.13 (5.16-7.34)	6.08 (5.14-7.21)	6.48 (5.43-7.87) *
Triacylglycerols (mmol/l)	1.68 (1.12-2.65)	1.59 (1.09-2.34)	2.51 (1.39-4.21) ***
AIP	0.06 (-0.15-0.33)	0.04 (-0.17-0.27)	0.29 (-0.05-0.67) ***
non HDL-C (mmol/l)	4.60 (3.69-5.82)	4.56 (3.63-5.67)	4.99 (4.06-6.41) **
LDL-C (mmol/l)	3.67 (2.79-4.63)	3.69 (2.88-4.58)	3.65 (2.64-5.02)
ApoB (g/l)	1.13 (0.93-1.37)	1.12 (0.91-1.35)	1.18 (1.00-1.45) *
HDL-C (mmol/l)	1.41 (1.15-1.73)	1.44 (1.19-1.75)	1.30 (0.99-1.67) **
ApoA1 (g/l)	1.52 (1.34-1.76)	1.53 (1.35-1.77)	1.49 (1.24-1.70) +
ApoB/ApoA1	0.74 (0.56-0.93)	0.72 (0.55-0.91)	0.83 (0.64-1.02) ***
Fasting glycemia (mmol/l)	5.00 (4.60-5.43)	4.94 (4.60-5.40)	5.10 (4.70-5.60) *
Insulin (mIU/l)	7.60 (5.30-10.90)	7.40 (5.30-10.6)	8.60 (5.00-13.43) +
HOMA-IR	1.68 (1.11-2.58)	1.63 (1.11-2.40)	1.99 (1.11-3.08) +
C-peptide (mg/l)	2.18 (1.53-2.98)	2.11 (1.50-2.88)	2.54 (1.76-3.53) **
Proinsulin (mIU/l)	11.00 (8.20-15.70)	10.8 (8.0-15.4)	11.9 (8.8-18.8) *

Data are expressed as median (1^{st}-3^{rd} quartile) with a p-value giving the statistical significance of the difference between smokers and non-smokers. + $p<0.05$, * $p<0.01$, ** $p<0.001$, *** $p<0.0001$, except of data about age that are expressed as mean ± standard deviation.

Table 2. Spearman correlation coefficient of AIP, ApoB/ApoA1 and nonHDL-C with parameters of insulin resistance in smokers and non-smokers.

	Fasting glucose	Insulin	HOMA-IR	C-peptide	Proinsulin
AIP					
in smokers	0.313**	0.521***	0.540***	0.510***	0.509***
(after adjustment)	0.091	0.121	0.137	0.110	0.073
in non-smokers	0.240***	0.353***	0.369***	0.447***	0.332***
(after adjustment)	0.092 +	0.129*	0.109*	0.220***	0.122*
in men	0.211**	0.433***	0.434***	0.489***	0.429***
in women	0.233***	0.355***	0.381***	0.455***	0.254***
ApoB/ApoA1					
in smokers	0.101	0.238*	0.255*	0.389***	0.263 *
(after adjustment)	0.050	0.001	0.036	0.252+	0.100
in non-smokers	0.145 *	0.214 ***	0.222***	0.220**	0.186***
(after adjustment)	0.010	0.036	0.009	0.019	0.029
in men	0.038	0.299***	0.278***	0.272***	0.258***
in women	0.163*	0.120+	0.147*	0.225***	0.092
nonHDL-C					
in smokers	0.310 **	0.093	0.158	0.234*	0.172
(after adjustment)	0.491 ***	0.112	0.137	0.022	0.095
in non-smokers	0.105+	0.148*	0.149*	0.166**	0.120 *
(after adjustment)	0.031	0.016	0.023	0.008	0.016
in men	0.143+	0.142+	0.151*	0.180*	0.125+
in women	0.154*	0.126+	0.143*	0.187**	0.109

+ $p<0.05$, * $p<0.01$, ** $p<0.001$, *** $p<0.0001$.

Discussion

In our study, we have tried to find out which of the used atherogenic indexes would correlate better with parameters of insulin resistance. AIP was found out to show stronger correlations than other indexes (ApoB/ApoA1 or non HDL cholesterol). The reason for this is probably the known correlation between glucose and triglyceride plasma levels, described already in 1983 by Pfeifer *et al.* AIP is the only index taking into account not only HDL cholesterol levels but also plasma TAG, that play the role of a regulator of lipoprotein interactions and not the role of an independent risk marker. This claim is supported by evidence that an increased plasma concentration of TAG is associated with an increased incidence of coronary artery disease. As mentioned above, high TAG and low HDL-C concentrations induce both an increase in small HDL particle and an increase in small, dense LDL particles (Dobiasova 2004), which is especially important in patients with insulin resistance. Thus, AIP has been found to be suitable and statistically reliable also in diabetics (Tan *et al.* 2004). We have shown that AIP correlates well with parameters of insulin resistance.

Nevertheless, after adjustment on age, BMI and waist circumference, power of these correlations was attenuated both in smokers and non-smokers and lost its statistical significance in smokers, suggesting higher importance of these factors. Both groups did significantly differ neither in age nor in BMI, but in waist circumference. We deduce that waist circumference drives this difference – being larger in smokers. Larger waist circumference reflects insulin resistance that is pronounced in smokers, and adjustment for waist circumference in them probably caused the loss of statistically significant correlation of AIP with parameters of insulin resistance. Another reason for loosing this correlation may be much smaller number of patients who smoked.

Larger waist circumference in smokers reflects

accumulation of visceral tissue in these patients. In concordance with our finding, it has been published that smokers have a higher tendency for accumulating visceral tissue (Nakanishi *et al*. 2014). In contrast with this finding, several studies report that smokers have a lower BMI than non-smokers (e.g. Pednekar *et al*. 2006). In our study, we have not found any statistically significant difference in BMI of smokers and non-smokers (although there was a tendency for higher BMI in smokers in contrast to non-smokers). Nevertheless waist circumference correlates better with the amount of visceral tissue than BMI and is nowadays accepted as a part of metabolic syndrome assessment.

Smoking is accepted as a major risk factor not only for metabolic but also for cardiovascular disease (Villablanca *et al*. 2000, Marshall *et al.* 2001, WHO 2002). It enhances cardiovascular risk factors such as elevated plasma triglycerides, decreases high-density lipoprotein cholesterol (HDL-C) and causes hyperglycemia (Criqui *et al.* 1980, Steiner *et al.* 1987, Tsiara *et al.* 2003). Our study confirms this well-established risk profile of smoking subjects – we showed that currently smoking patients developed proatherogenic changes in their lipidograme. Smoking also reduced insulin sensitivity, which has already been shown by some other authors (e.g. Targher *et al.* 1997, Lathi-Koski *et al.* 2002, Li *et al.* 2012). Li *et al.* (2012) have found difference between the smoking and non-smoking participants in insulin resistance, but this difference was not significant after adjustment for BMI. Fasting serum insulin levels gradually increased with increasing BMI. We also have found waist circumference as the major and most significant predictor of high insulin and glucose levels. These relations between insulin resistance and obesity are currently intensively studied (Novotny *et al.* 2014).

We are aware that our study has several limitations. We have not used equally large gender and age matched groups for comparing group of smokers and non-smokers. In order to determine insulin resistance we have used HOMA-IR but not golden standard – euglycemic hyperinsulinemic clamp. On the other hand HOMA-IR is suitable for daily praxis because it does not involve intravenous infusion, only simple calculation. HOMA-IR model has proved to be a robust clinical and epidemiological tool for the assessment of insulin resistance (Singh *et al.* 2010) and it is more frequently used than another index – so called QUICKI (Quantitative insulin sensitivity check index) (Katz *et al.* 2000).

We conclude that AIP can be used in daily praxis in patients with dyslipidemia, predominantly in non-smokers, as a predictor of insulin resistance. It is a simple and easily accessible laboratory parameter that correlates with markers of insulin resistance and does not need assessing of insulin level. We also showed, that smoking enhances proatherogenic lipid profile, accumulation of visceral tissue and insulin resistance and its repression is a desirable public health goal.

Conflict of Interest

There is no conflict of interest.

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Abbreviations

AIP, atherogenic index of plasma; TAG, triacylglycerols; HDL-C, high density lipoprotein cholesterol; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; non HDL-C, TC – HDL-C; ApoB, apolipoprotein B; ApoA1, apolipoprotein A1; HOMA-IR, homeostatis model assessment – insulin resistance; BMI, body mass index; OR, odds ratio.

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