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The association between aspirin resistance and extend and severity of the coronary atherosclerosis

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ABSTRACT

OBJECTIVE: Uncontrolled inflammatory responses could contribute to pathogenesis of many leading causes of human morbidity and mortality. Aspirin is an antiinflammatory and antithrombocytic drug which is used in the primary and secondary protection in atherothrombotic diseases and complications. The aim of this study was to analyze the effect of aspirin resistance in the extend and severity of atherosclerosis.

METHODS: 100 patients who underwent coronary angiography with suspected or known coronary artery disease and using aspirin were enrolled into the study.

RESULTS: Of these 100 patients; 30 (8 female, 22 male) formed aspirin resistant group (ARG) and 70(22 female, 48 male) formed control group. Gensini scoring system (GSS) was significantly higher in ARG than control group (80.5 (36–166) vs. 45 (2–209); p<0.001). Number of percutaneous coronary intervention (PCI) patients was significantly higher in ARG group [13 of 30 (%43.3) ARG group vs. 13 of 70 (%18.6) control group; p=0.01]. Furthermore; when we evaluate the 16 reintervention patients, stent restenosis was significantly higher in ARG (11 of 16 (%68.75) ARG vs. 5 of 16 (%31.25) control group; p=0.016). Multivariate logistic regression analysis revealed that, GSS (p=0.038; %95 CI:1.001–1.026) and PCI history (p=0.017; %95 CI: 1.182–89.804) were independent risk factors for aspirin resistance.

CONCLUSION: Our study concluded that; atherosclerotic burden calculated by GSS is significantly higher in aspirin resistant patients. According to this result, we suggest that aspirin treatment can be prescribed in higher doses in aspirin resistance patients with coronary events. Furthermore GSS and PCI history could be independent predictors of aspirin resistance.

Keywords: Aspirin resistance; atherosclerosis; coronary artery disease.

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Uncontrolled inflammatory responses could contribute to the pathogenesis of many leading causes of human morbidity and mortality [1]. Atherosclerosis, a chronic low grade inflammatory state, is one of the most common causes of death in developed countries and an example of uncontrolled inflammation [2]. Clinical importance of atherosclerosis attracts many attention to the inflammation cascade. Arachidonic acid is a polyunsaturated fatty acid which accounts for 10–20% of the phospholipid fatty acid content on average [3]. Metabolites produced by the oxygenation of the arachidonic acid play the key role in modulation of inflammation [4]. Cyclooxygenase (COX) and lipoxygenase (LOX) enzyme families degrade arachidonic acid to various proinflammatory metabolites. Thrombaxane-A2, which propogates strong vasoconstriction and platelet aggregation, is synthesized by COX-1 [5]. COX-2 enzyme catalyzes prostocyclin, one of the strongest vasodilator metabo-

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lites, synthesis reaction [6]. Second important pathway producing eicosonoids is catalyzed by LOX enzyme family. Leucotriene-B4 produced by this pathway is a known mediator of programmed apoptosis and atherosclerosis [7]. As a result of this close relation between arachidonic acid metabolites and endothelial homeostasis, these enzymatic pathways deserve great attention.

Aspirin is an important antiinflammatory drug that directly inhibits COX enzyme family. It is an effective antithrombocytic drug which is used in the primary and the secondary protection in atherothrombotic diseases and complications [8, 9]. Aspirin resistance is of import on atherosclerosis. Two types of aspirin resistance defined. The occurence of new cardiovascular events in the patients who are using aspirin is defined as "clinical resistance" and incomplete blockage of platelet activity in vitro is defined as "laboratory resistance" [10]. Because there is a well known close relation between atherosclerosis and inflammation, antiiflammatory drugs inhibiting certain steps of arachidonic acid pathway and resistance to them become trend topics of cardiology. The main purpose of this study was to analyze the association between aspirin resistance and extend and severity of the coronary atherosclerosis.

MATERIALS AND METHODS

Patient Population

One hundred patients were included in this study between 01.04.2013 and 30.11.2013 with suspected coronary artery disease (CAD) due to typical chest pain or positive noninvasive cardiovascular stress testing who underwent cardiac catheterization. Exclusion criteria were defined as: thrombocytopenia (<100000/mm^3), thrombocytosis (>400000/mm^3), end stage renal disease (ESRD), acute or chronic liver failure, hematologic diseases, history of malignant disease, active infection, intolerance or contraendication to aspirin, being under the treatment of glycoprotein IIbIIIa inhibitors in last 3 days, usage of antithrombotic or anticoagulant treatment other than aspirin in last 30 days, regular use of nonsteroidal antiinflammatory treatment in last 3 months, subjects younger than 30 and older than 75 years old. After application of exclusion criteria 100 patients with known or newly diagnosed CAD already using therapeutic doses of aspirin were included.

Study protocol

The study was designed as a prospective observational study. Basic demographic data of the enrolled patients included age, gender, body mass index (BMI), glomerular filtration rate (GFR), presence of traditional major cardiovascular risk factors (age, sex, hypertension, diabetes, dyslipidemia, family history of premature cardiovascular disease (CVD), and current smoking). Extend and severity of atherosclerosis was analysed with the help of Gensini scoring system (GSS) [11]. Afterwards, venous blood samples were taken for the biochemical analysis. The study was approved by Istanbul Bilim University local ethics committee with the number 44140529/2013–028. All patients were informed about the study and written informed consents were obtained.

Angiographic evaluation

Angiographic evaluations were done by 2 different experienced cardiologists. The extend and severity of CAD were assessed by the GSS. The Gensini score was calculated by multiplying the severity coefficient assigned to each coronary stenosis according to the degree of luminal narrowing (reductions of 25%, 50%, 75%, 90%, 99%, and complete occlusion were given Gensini scores of 1, 2, 4, 8, 16, and 32, respectively) by the coefficient identified, based on the functional importance of the myocardial area supplied by that segment as follows: Left main coronary artery, 5; proximal segment of left anterior descending coronary artery, 2.5; mid segment of left anterior descending coronary artery, 1.5; apical segment of left anterior descending coronary artery, 1; first diagonal branch, 1; second diagonal branch, 0.5; proximal segment of circumflex artery, 2.5 (if right coronary artery dominancy existed 3.5); distal segment of circumflex artery, 1 (if dominant, 2); obtuse marginal branch, 1; posterolateral branch, 0.5; proximal segment of right coronary artery, 1; mid segment of right coronary artery, 1; distal segment of right coronary artery, 1; and posterior descending artery, 1.

Biochemical Analysis

After stopping the oral intake for 8–12 hours blood samples, that are drawn from the brachial veins of all the patients are injected into dry tubes and the samples are centrifuged before biochemical evaluation. Total cholesterol (TC), low density lipoprotein (LDL), very low density lipoprotein (VLDL), high density lipoprotein (HDL), triglyceride (TG), fasting blood glucose, blood urea nitrogen (BUN), creatinine, complete blood count (CBC) were measured.

In our study aspirin resistance is evaluated with "VerifyNow" system which is an adenosine diphosphate (ADP) stimulation method. Aspirin inhibition levels are detected by taking blood from the patients who are taking therapeutic dose aspirin (at least 100 miligram(mg)/day) after 12–24 hours. "VerifyNow" is a system which is based on the stimulation of fibrinogen coated particals in full blood with citrate, by agonists like ADP, thrombin receptor activating peptide (TRAP), and arachidonic acid in mixing compartment. By adding the anticoagulated blood into the mixing compartment platelets are activated and platelet aggregation occures after the bonding between GPIIb/IIIa receptors on activated platelets and particles with fibrinogen. After this reaction the change of light transmittions is defined as aspirin reaction unit (ARU). ARU>550 is considered as aspirin resistance [12, 13].

Statistical Analysis

In this study, all statistical analysis were performed with SPSS 16.0 software (Statistical Package for the Social Sciences, SPSS inc, Chicago IL). Fitness to normal distrubition was analysed with the Kolmogorov-Simirnov test. Homogenity of variances was calculated with the Levene test and the Lilliefors significance correction. Inter-observer agreement between 2 cardiologists was calculated using Bland-Altman analysis. Differences among two groups were analysed by the Student's t test or its non-parametric counterpart, Mann Whitney-U test. Categorical variables were analysed by either Chi-square test or Fisher's exact test where appropriate. Multivariate logistic regression analysis were performed to explore the factors effecting aspirin resistance. Data expressed as mean±standard deviation. Differences were considered statistically significant at p<0,05.

RESULTS

One hundred patients who underwent coronary angiography with suspected or known CAD and using aspirin were enrolled into the study. Clinical and demographical characteristics of over all subjects are given in Table 1.

Of these 100 patients; 30 (8 female, 22 male) formed aspirin resistant group (ARG) and 70 (22 female, 48 male) formed control group. There were no statistically significant differences in age, smoking, diabetes mellitus (DM), hypertension (HT), BMI, GFR levels, beta blocker, angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), statin usage between ARG and control groups. Only LDL level was significantly higher in ARG group as shown in Table 2.

Table 1. Clinical and demographic characteristics of over all subjects

n=100	%
Age (years old)	62.72±7.93
Gender (female)	30
Diabetes mellitus	45
Hypertension	75
Hyperlipidemia	95
Smoking	32
Stent history	26

There was statistically nonsignificant difference in GSS between 2 cardiologists (p=0.76). GSS was significantly higher in ARG than control group (80.5 (36–166) vs. 45 (2–209); p<0.001) as shown in Figure 1.

Beside this, 26 of total 100 patients had first or repetitious percutaneous coronary intervention (PCI) history. There were no acute stent thrombosis patients, 10 patients (38.5%) had first PCI, 16 patients (61.5%) had reintervention because of stent restenosis. Number of PCI patients was significantly higher in ARG group [13 of 30 (43.3%) ARG group vs. 13 of 70 (18.6%) control group; p=0.01]. Furthermore; when we evaluate the 16 reintervention patients, stent restenosis was significantly higher in ARG group [11 of 16 (68.75%) ARG group vs. 5 of 16 (31.25%) control group; p=0.016] as shown in Table 3. There were statistical significant in LDL levels, GSS and stent thrombosis between ARG and control groups. However, multivariate logistic regression analysis revealed that, only GSS (p=0.038; 95% CI:1.001–1.026) and PCI history (p=0.017; 95% CI: 1.182–89.804) were independent risk factors for aspirin resistance as shown in Table 4.

DISCUSSION

In our recent study we aimed to investigate the association between aspirin resistance and extend and severity of the coronary atherosclerosis. Anti-platelet therapy remains most important and effective management in prevention of important clinical complications of atherothrombosis

Table 2. Comparison of baseline characteristics of ARG and control groups

Parameter	ARG (n=30) Mean±SD		Control (n=70) Mean±SD		p
	n	%	n	%	
Age (years old)*	63.3±6.70		62.47±8.43		0.635
Female gender†	8	26.7	22	31.4	0.634
Smoking†	10	33.3	22	31.4	0.852
Diabetes mellitus†	15	50	30	42.9	0.511
Hypertension†	22	73.3	53	75.7	0.601
Beta blocker†	13	43.3	43	61.4	0.095
ACE inhibitor†	7	23.3	22	31.4	0.414
Statin†	10	33.3	25	35.7	0.819
PPI†	5	16.7	6	8.6	0.236
BMI (kg/m^2)*	27.12±1.29		26.85±1.51		0.402
GFR (ml/min)*	87.08±27.92		79.92±18.04		0.129
LDL (mg/dl)*	128.33±43.40		108.43±40.02		**0.029**

ARG: Aspirin resistant group; ACE: Angiotensin converting enzyme; PPI: Proton pump inhibitor; BMI: Body mass index; GFR: Glomerular filtration rate; LDL: Low density lipoprotein; *Student's t test; †Chi-square test.

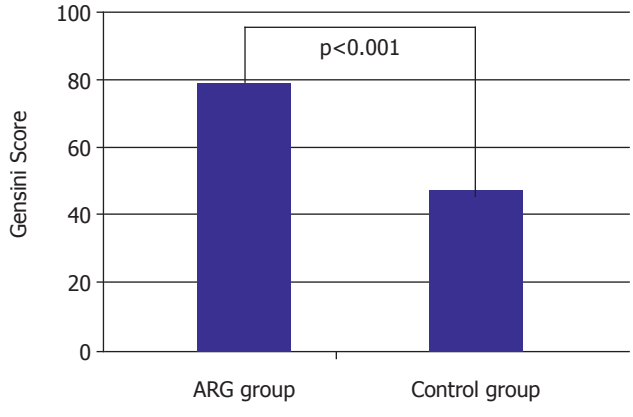

Figure 1. Comparison of Gensini score between aspirin resistance and nonresistance group. ARG: Aspirin resistance group

Table 3. Clinical and demographic characteristics of over all subjects

Parameter	ARG (n=30)	Control (n=70)	p
Aspirin dose (mg/day)*	100 (100–300)	100 (80–300)	**0.018**
Gensini score*	80.5 (36–166)	45 (2–209)	**<0.001**
Number of total PCI†	13 (%43.3)	13 (%18.6)	**0.01**
Number of reintervention†	11 (68.75%)	5 (31.25%)	**0.016**

ARG: Aspirin resistant group; PCI: Percutaneous coronary intervention; *Mann Whitney- U test; †Student's t test.

namely acute coronary events, cerebral vascular accidents and all other thrombotic events [7]. Aspirin is an important anti-platelet and anti-inflammatory drug which is fairly well analysed ever. In the meta-analysis of 5 randomized studies that include 9853 patients who were followed with stable cardiovascular disease, 21% decrease in cardiovascular event risk (nonfatal myocardial infarction (MI), nonfatal stroke and cardiovascular death) and 13% decrease in all cause mortality were found in the patients who were taking low dose aspirin (75–325 mg/day) [14]. In a review that includes 287 randomized controlled studies with more than 200000 patients (Antithrombotic Trialists' Collaboration) 22% decrease in the risk of cardiovascular event mortality was detected [9]. Effectiveness of regular aspirin usage in reducing risk for myocardial infarction, ischemic stroke, and fatal coronary events among patients with preexisting atherosclerotic cardiovascular diseases is well established [15]. Although cheap, effective and easily accessible, aspirin resistance

Table 4. Logistic regression analysis giving information about the independent risk factors for aspirin resistance

Parameter	Beta	p	CI (95%)
Gensini score	0.013	**0.041**	**1.001–1.026**
LDL (mg/dl)	0.012	0.073	0.999–1.025
PCI history	2.206	**0.034**	**1.182–89.804**
Aspirin dose (mg/day)	-0.009	0.062	0.991–0.997

CI: Confidence interval; LDL: Low density lipoprotein; PCI: percutaneous coronary intervention.

restricts the usage of this anti-platelet and anti-inflammatory drug. Aspirin resistance defined as the incapacity of aspirin to decrease platelet production of thromboxane-A2 and so platelets activate and aggregate [16]. Prevelance of aspirin resistance has been estimated between 5% to 60% of aspirin treated patients for secondary prevention [17]. That's why patients treated with aspirin still retain at substantial risk of clinically important cardiovascular diseases, due to insufficient inhibition of platelet aggregation via thromboxane-A2 pathway. The incidence of aspirin resistance was found 30% in our study which is compatible with previous ones. It is obvious that, patients having aspirin resistance are prone to atherothrombotic and atherosclerotic events. Krasopoulus et al. reported that, long term aspirin treated patients who are resitant to aspirin are at a greater risk of important cardiac morbidity than patients who are sensitive to aspirin [18].

As we mentioned previously, atherosclerosis is a chronical low grade inflammatory state. Aspirin, due to the COX enzyme inhibitor activity, is also a well known anti-inflammatory drug. Influence of inflammation on the progression of atherosclerosis and rupture of atherosclerotic plaque opens a new therapeutic era for atherosclerosis. Not only aspirin, but also some other drugs such as statins, thiazolidinedions (glitazones), and renin angiotensin aldosterone system blockers exert their anti-atherosclerotic effect through modulation of endothelial inflammation [19, 20]. Beside this, in a recent study it was found that anti-platelet agents, namely aspirin, clopidogrel or ticagrelor, significantly reduces high sensitive C reactive protein level, which is a key biomarker of inflammation [21]. In our study there was no significant difference in statin and renin angiotensin aldosteron system blocker usage between ARG and control group that can affect inflammatory state. Furthermore, in a similar study Li et al. showed that, anti-inflammatory effect of tanshinone IIA, one of the most abundant constituents of the root of the red sage, improves inflammation and increases atherosclerotic plaque stability [22]. In the light of foregoing data; it is known that atherosclerosis is one of the reason of inflammatory state and anti-inflammatory agents such as aspirin could exert anti-atherosclerotic effect. We might conclude that, patients having aspirin resistance could be more prone to atherosclerosis and atherothrombosis. As far as we see, there is hardly any literature assessment to analyze the relationship between GSS and aspirin resistance. In our study, we revealed that GSS was significantly higher in aspirin resistant patients which means that atherosclerotic burden is significantly higher in aspirin resistance. Furthermore, we also found that coronary reintervention ratio is significantly higher in ARG group. We consider that, aspirin has anti-platelet and anti-inflammatory effects and in aspirin resistance patinets lack of these effects are the possisble reasons of high GSS and coronary reintervention ratio.

Although possible merchanisms of aspirin resistance are beyond the scope of this article, effect of aspirin dose on aspirin resistance could be discussible. Actually, in a study Gengo et al. demonstrated that patients who are nonresponsive to 81 mg/day dose of aspirin became responsive at 162 mg/day or greater dose [23]. In a similar study, Duzenli et al. revealed that increasing the aspirin dose to 300 mg/day or adding clopidogrel to aspirin can provide adequate platelet inhibition in a significant number of patients with impaired responses to low dose aspirin [24]. Interestingly, in our study mean aspirin dose in control group was significantly higher than ARG group. In mentioned previous studies nonresponsive patients became aspirin responsive at doses higher than 150 mg/day. In our study, although both groups' aspirin doses were in therapautic ranges they were not in maximal doses. This could be the possible reason of this result.

Prothrombotic and inflammatory state is related with aspirin resistance in hyperlipidemic patients and it is known that this relation is not depernd on LDL cholesterol levels. In our study LDL level was significantly higher in ARG group. However, there were some other factors such as statin usage and other causes of inflammatory state could effect aspirin resistance [25].

Conclusion

Our study concluded that; atherosclerotic burden calculated by GSS is significantly higher in aspirin resistant

patients. According to this result, we suggest that aspirin treatment can be prescribed in higher doses in aspirin resistance patients with coronary events. Furthermore, gensini score and PCI history could be independent predictors of aspirin resistance. Absolutely, higher scaled researches are needed for further elucidate the clinical implications of these findings.

Limitations of the Study

One of the limitations was the lack of basal aspirin reaction unit (ARU) before aspirin treatment. However all the patients was evaluated by VerifyNow and ARU levels were obtained under therapeutic dose aspirin treatment, cut off level was 550, which is considered as a critical level in most studies. This provides us to get over this limitation in a way. Another limitation was the small number of subjects in ARG group. And also low dose of aspirin was used in ARG than control group but both of them were in therapeutic ranges.

Conflict of Interest: The authors declare no conflict of interest.

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