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Original Article

Effect of low-dose aspirin on platelet aggregation inhibition in patients with rheumatoid arthritis

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Abstract

Introduction: The risk for coronary artery disease (CAD) and mortality has increased in patients with rheumatoid arthritis (RA). Aspirin has anti-thrombotic effects and causes reduction in CAD occurrence in high-risk individuals. The objective of present project was evaluating the influence of low-dose aspirin on inhibition of platelet aggregation in patients with RA.

Methods: Forty-eight subjects with RA diagnosed based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria and age- and sex-matched healthy participants were studied. All subjects received 81 mg/day aspirin for 10 days. Level of the serum thromboxane B2 (sTxB2), a permanent metabolite of thromboxane A2 (TxA2), was measured before and after therapy using enzyme-linked immunosorbent assay (ELISA) kit. The impotency to decrease sTxB2 production to less than 10 ng/ml indicates suboptimal suppression of platelet aggregation via aspirin.

Results: Low-dose aspirin decreased sTxB2 significantly compared with baseline in patients with RA [median interquartile range (IQR): 25.72 (11.78, 90.10) to 7.74 (5.80, 8.82), $P < 0.001$] and in healthy controls [median (IQR): 40.50 (33.25, 50.90) to 7.30 (4.75, 8.85), $P < 0.001$]. No remarkable changes were seen in sTxB2 between patients and controls after adjustment ($P > 0.050$). Pharmacologic influence of aspirin was suboptimal in 6.25% of cases in the presence of higher erythrocyte sedimentation rate (ESR) and in 2.7% of controls. Low-dose aspirin decreased sTxB2 significantly only in patients with Framingham Risk Score (FRS) < 10%.

Conclusion: Low-dose aspirin decreased sTxB2 level and suppressed platelet aggregation and therefore, was effective in primary prevention of cardiovascular (CV) events in patients with RA; however, additional studies are required to reach accurate conclusions.

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Introduction

Rheumatoid arthritis (RA) is a type of systemic disorder specified with inflammation, tenderness, and advanced joints damage, leading to inability and higher death rates.[1] RA is related with various cardiovascular (CV) events.[2] Patients with RA are at high risk of mortality in comparison with general community mainly attributed to atherosclerosis, particularly coronary artery disease (CAD). It is indicated that CAD accounts for about 40%–50% of deaths in patients with RA. In order to calculate the high CAD risk caused by RA, the European League Against Rheumatism (EULAR) suggested models of CAD risk score, adjusted for patients with RA by proposing a 1.5 multiplication factor whenever the patient has 2 out of 3 criteria including: duration of disease ≥ 10 years, positive rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP) antibodies, and demonstrating extra-articular signs.[3]

Low-dose aspirin was demonstrated to be

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helpful for preventing from thrombosis and CAD in the general population and is almost universally recommended.[4-7] Previous studies reported that aspirin therapy had less effect in patients with systemic lupus erythematosus (SLE) but suppressed serum thromboxane B2 (sTxB2) and led to significantly lower TxB2 excretion in control subjects.[8,9] Another study on patients with RA, who were at high risk for CAD, confirmed underutilization of aspirin.[10] Main mechanism by which aspirin exerts its effect against thrombosis is irreversible inhibition of cyclooxygenase-1 (COX-1), and therefore, inhibition of platelet TxA2 synthesis and consequently suppression of platelet reactivity.[11] sTxB2, a permanent product of TxA2, is the sole parameter that particularly evaluates the influence of aspirin on COX-1 activity.[12] It is indicated that reduction in sTxB2 to less than 10 ng/ml is correlated with ≥ 95% platelet aggregation suppression.[13] Accordingly, levels of sTxB2 ≥ 10 ng/ml following aspirin therapy are supposed a threshold to state aspirin's suboptimal action.[14,15]

To the authors' knowledge, no studies investigated the effect of aspirin on suppression of Tx biosynthesis in patients with RA; therefore, considering the antithrombotic effects of aspirin in normal individuals as well as the scarcity of data about aspirin response in RA and in an effort to discover new approaches aimed at alleviating CAD risk and mortality in RA, current study was performed to assess the effects of low-dose aspirin on suppression of platelet aggregation in patients with RA.

Methods

In this study, effects of consuming aspirin with low-dose were compared between patients with RA and healthy control subjects. Our sample size was calculated based on study by Kawai et al.,[9] considering sTxB2 concentration. Taking into account a 95% confidence level (CI) and 80% power, the sample was estimated at least 45 cases in each group. In the present study, 48 subjects aged 30-75 years with RA diagnosis based on the ACR/EULAR 2010 criteria[16,17] with disease duration > 6 months were included from the rheumatology section of Tabriz University of Medical Sciences, Tabriz, Iran, between September 2017 and February 2018. Additionally, age- and sex-matched healthy control subjects without any inflammatory rheumatic disorders were selected. Our criteria for excluding subjects were: age < 18 years old, taking anticoagulants and/or antiplatelet medicines, being sensitive to aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), peptic ulcers, tendency to lose blood, kidney insufficiency (serum creatinine more than 1.8 mg/dl, proteinuria ≥ +2 on dipstick), lower platelet counts (< 100000/µl), or pregnant women. Subjects were asked not to use NSAIDs for at least one week before the baseline visit and during the study. This study was accepted by the Ethics Committee of Tabriz University of Medical Sciences and all subjects signed informed consent before inclusion in the research. Furthermore, this study was recorded on the Iranian Registry of Clinical Trials (IRCT) website (code: IRCT201707293812N6).

At baseline, a rheumatologist examined all participants and the Disease Activity Score-28 (DAS-28) measure of disease activity and Simple Disease Activity Index (SDAI) were recorded for patients with RA. Afterwards, all subjects received 81 mg/day aspirin for 10 days. Samples were requested not to use aspirin 10 days prior to the first study visit. Any person that stated aspirin consumption or had a sTxB2 level less than 10 ng/ml at baseline, was considered to be aspirin consumer.

Furthermore, anthropometric measurements including body weight, height, and waist circumference (WC) were assessed and body mass index (BMI) was obtained via dividing weight (in kilograms) by the square of height (in meters).[18]

Blood pressure was evaluated twice with subject sitting down in a resting position, after a 5-minute rest, via a sphygmomanometer, and the mean of two measurements was declared.

At the start and at the end of study, 5 ml of fasting blood samples were obtained. Then serum samples were separated and stored at −70 °C until biochemical analysis. Serum TxB2 was determined with an enzyme-linked immunosorbent assay (ELISA) kit (Abnova Corporation, Taiwan) and an ELISA plate reader (Model stat fax 2100, Awareness, Ramsey, MN). Other analytical evaluations included a complete blood count (CBC), serum total cholesterol (TC), high-density and low-density lipoprotein cholesterol (HDL-C and LDL-C), triglyceride (TG), fasting blood sugar (FBS), anti-CCP, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Serum glucose, TC, TG, HDL-C, and LDL-C were determined via enzymatic colorimetric procedure using Pars Azmoon kits (Pars Azmoon Inc., Tehran, Iran). Serum anti-CCP (Medizym) and CRP (Monobind) were measured by ELISA methods.

Presence of three or more of the following criteria is necessary for being classified as a metabolic syndrome (MetS):[19] WC above ethnicity-specific value, TG ≥ 150 mg/dl, HDL-C less than 40 mg/dl in men and less than 50 mg/dl in women, systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg, and FBS ≥ 100 mg/dl.

SPSS software (version 18, SPSS Inc., Chicago, IL, USA) was used for analyzing data. Kolmogorov-Smirnov test (K-S test) was selected for evaluating normality distribution of data. Pre- and post-differences between variables were compared by Wilcoxon signed-rank test. Baseline comparisons between groups were assessed with Mann-Whitney U test. At the end of the study, analysis of covariance (ANCOVA) was used to find differences between two groups, adjusting for baseline values. Spearman's rank correlation analysis was used for analyzing correlations between variables. Statistical significance was defined as $P < 0.05$.

Results

Our study groups did not vary regarding age, sex, ethnicity, BMI, TG, and HDL-C. RA cases were more susceptible to present hypertension (HTN), MetS, and high ESR and CRP levels compared with controls. General, clinical, and biochemical features of study patients are illustrated in table 1. Based on our study, 46 (96%), 44 (92%), and 40 (83%) patients used prednisolone, methotrexate, and hydroxychloroquine, respectively. Also, 20 (41%), 5 (10%), and 2 (4%) patients used sulfasalazine, leflunomide, and anti-tumor necrosis factor alpha (anti-TNF-α) agents, respectively.

Table 1. General, clinical, and biochemical characteristics of patients with rheumatoid arthritis (RA) (n = 48)

Characteristic	Mean ± SD
Age (year)	54.79 ± 9.73
Disease duration (year)	10.47 ± 8.11
BMI (kg/m^2)	30.15 ± 4.09
WC (cm)	104.06 ± 10.21
ESR (mm/hour)	25.91 ± 14.08
DAS-28	3.68 ± 0.66
SDAI	15.71 ± 5.12
SBP (mmHg)	126.35 ± 13.32
DBP (mmHg)	81.67 ± 3.77
FBS (mg/dl)	103.89 ± 34.69
TG (mg/dl)	145.75 ± 38.18
HDL-C (mg/dl)	45.04 ± 10.07
LDL-C (mg/dl)	138.27 ± 30.41
TC (mg/dl)	212.46 ± 32.11
FRS (%)	3.64 ± 2.90

BMI: Body mass index; WC: Waist circumference; ESR: Erythrocyte sedimentation rate; DAS-28: Disease activity score 28; SDAI: Simple disease activity index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; TG: Triglyceride; LDL-C: Low–density lipoprotein cholesterol; HDL-C: High–density lipoprotein cholesterol; TC: Total cholesterol; FRS: Framingham risk score; SD: Standard deviation

Table 2 demonstrates sTxB2 before and after aspirin therapy in patients with RA and healthy controls. As indicated in table 2, no statistically significant change was observed between the two groups regarding serum TxB2 at the beginning of study ($P > 0.050$). Significant reduction occurred in serum levels of TxB2 in both RA patients ($P < 0.001$) and healthy controls ($P < 0.001$) after 10 days of aspirin therapy (Table 2). After study, no significant difference was found between two groups in sTxB2 levels ($P > 0.050$) after adjusting for baseline values (Table 2).

Table 2. Comparison of serum thromboxane B2 (sTxB2) in treatment groups before and after aspirin therapy

Variable	Measurement period	RA patients (n = 48)	Control group (n = 48)	P**
sTxB2 (ng/ml)	Baseline	25.72 (11.78, 90.10)	40.50 (33.25, 50.90)	0.126
	After 10 days	7.74 (5.80, 8.82)	7.30 (4.75, 8.85)	0.610
P*		< 0.001	< 0.001	

Data were presented as median (IQR)
*Wilcoxon signed-rank test; **Mann-Whitney U test at baseline or analysis of covariance (ANCOVA) test, adjusted for baseline values after 10 days; P < 0.05 was considered statistically significant
sTXB2: Serum thromboxane B2; RA: Rheumatoid arthritis

The pharmacologic effect of aspirin was suboptimal in 6.25% of patients and 2.70% of controls.

According to table 3, 25% of patients were classified as overweight and 68.8% of patients were obese. Hypertriglyceridemia, hypercholesterolemia, and MetS were present in 45.8%, 66.7%, and 37.5% of patients, respectively. Moreover, anti-CCP was positive in 85.4% of patients and the majority of patients (94.0%) had Framingham Risk Score (FRS) less than 10.0%. As indicated in table 3, low-dose aspirin led to significant decrease in sTxB2 level in overweight (P = 0.002) and obese patients with RA (P < 0.001) as well as in subjects with MetS (P < 0.001) and without MetS (P < 0.001).

Table 3. Comparison of serum thromboxane B2 (sTxB2) in patients with rheumatoid arthritis (RA) before and after aspirin therapy (n = 48)

Variable	sTxB2 (ng/ml)		P*
	Baseline	After 10 days	
BMI (kg/m^2)			
< 25 (n = 3)	12.40 (11.45, 12.50)	8.62 (8.50, 9.30)	0.109
25-29.9 (n = 12)	67.39 (19.40, 93.77)	8.80 (7.85, 9.18)	0.002
≥ 30 (n = 33)	16.50 (11.45, 82.21)	6.30 (5.46, 8.59)	< 0.001
TG (mg/dl)			
≤ 150 (n = 26)	41.94 (11.40, 93.97)	8.48 (5.62, 9.23)	< 0.001
> 150 (n = 22)	16.23 (12.33, 48.63)	6.89 (5.80, 8.42)	< 0.001
HDL-C (mg/dl)			
≥ 40 (n = 22)	20.40 (11.44, 48.63)	7.25 (6.20, 8.92)	< 0.001
< 40 (n = 26)	37.47 (12.39, 93.75)	7.79 (5.64, 8.89)	< 0.001
DAS-28			
2.6-3.1 (n = 12)	18.30 (11.45, 37.58)	7.90 (5.32, 8.80)	0.002
3.2-5.1 (n = 36)	48.09 (12.43, 93.30)	7.50 (5.80, 9.04)	< 0.001
> 5.2 (n = 0)	-	-	-
CRP (mg/l)			
≤ 6 (n = 29)	16.50 (12.35, 65.55)	7.20 (5.75, 8.79)	< 0.001
> 6 (n = 19)	42.48 (11.40, 93.90)	8.30 (5.89, 9.11)	< 0.001
ESR (mm/hour)			
< 30 (n = 36)	15.23 (11.61, 48.23)	6.75 (5.52, 8.59)	< 0.001
> 30 (n = 12)	93.76 (32.33, 96.50)	8.97 (8.33, 11.15)	0.002
Anti-CCP			
Positive (n = 41)	40.70 (11.61, 92.62)	7.20 (5.75, 8.80)	< 0.001
Negative (n = 7)	24.30 (12.40, 28.20)	8.77 (8.50, 9.45)	0.018
FRS (%)			
< 10 (n = 45)	16.50 (11.61, 82.21)	7.70 (5.80, 8.97)	< 0.001
10-20 (n = 3)	94.40 (93.34, 95.30)	7.77 (6.30, 8.40)	0.109
> 20 (n = 0)	-	-	-

Data were presented as median (interquartile range or IQR); *Wilcoxon signed-rank test
sTXB2: Serum thromboxane B2; BMI: Body mass index; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; DAS-28: Disease activity score 28; CRP: C-reactive protein; Anti-CCP: Anti-cyclic citrullinated peptide; ESR: Erythrocyte sedimentation rate; FRS: Framingham risk score

Moreover, based on DAS-28, sTxB2 level decreased significantly in RA patients with low disease activity (P = 0.002) and moderate disease activity (P < 0.001) as well as in patients with either positive anti-CCP (P < 0.001) or negative anti-CCP (P = 0.018) after 10 days of low-dose aspirin treatment. Furthermore, low-dose aspirin decreased sTxB2 level significantly only in patients with FRS < 10% (P < 0.001). Moreover, sTxB2 level did not differ significantly based on patients' medications.

Discussion

In the current study, we compared aspirin response in RA cases and control subjects for the first time. Our study noted that serum TxB2 decreased significantly in both RA cases and healthy controls after 10 days aspirin therapy. In other words, aspirin suppressed platelet production of sTxB2 to less than 10 ng/ml, which was associated with ≥ 95% suppression of platelet aggregation[13] in 90% of patients with RA and in 94% of the control subjects. Since determination of sTxB2 level in whole blood lets clot assess the capacity of highly active platelets to produce Tx, thus, sTxB2 measure is the most precise and proper way to evaluate the aspirin pharmacologic properties and is the most permanent measure to describe reflection to aspirin.[20-22]

There have been no other studies evaluating the aspirin response in patients with RA; therefore, we compared present findings with results of previous studies carried out in other patient groups. In a study by Kawai et al.,[9] aspirin almost completely suppressed sTxB2 in control subjects, but had less effect in SLE cases. Current study was not in line with Kawai et al.[9] that reported that effect of aspirin was suboptimal in 15% (5/34) of the SLE participants but not in control subjects. Furthermore, response to aspirin was lower than optimal in the presence of MetS and high serum CRP level.[9] It should be noted that SLE is more hyper-coagulation state in comparison with RA, and therefore, it can be considered as a potential risk factor for aspirin resistance.

Based on our study, only high ESR level had the significant correlation with suboptimal response to aspirin in patients with RA. Moreover, response to aspirin was lower in patients with FRS between 10%-20% compared to patients with FRS below 10%.

Our study was in contrast with previous investigations using urinary 11-dehydro-TxB2 (Tx-M) which indicated a probably disrupted response to aspirin in patients with SLE.[8,23,24] In another study, 80% inhibition in urinary excretion of Tx-M following aspirin consumption (50 mg/day for one week) was reported in subjects with SLE, but most patients had urine Tx-M levels after receiving aspirin that were greater than the median value for controls who were not consuming aspirin.[23] Furthermore, in a research by Avalos et al.,[8] urinary Tx-M did not change considerably in patients with SLE who declared using or not using aspirin, indicating damaged responses to aspirin. However, metabolites in urine do not reflect a particular eicosanoid biosynthesis site and urine Tx-M is not an authentic marker of aspirin action on platelets.[25,26] Additionally, various tests examine different facets of aspirin reaction[14,22] like Tx generation from sources independent of extra-platelet and COX-1.[14,24,27-29] Overall, one of the most particular tests for pharmacological action of aspirin is sTxB2 suppression.[21,22] In another study by Smith et al.,[25] MetS had strong association with less effective COX-1 inhibition. This controversy between findings from different studies might be because of variations in studied individuals, physiological circumstances (e.g., different types of disease), disease duration, baseline TxB2 status, dosage and duration of aspirin therapy, variation between individuals in reaction to aspirin, and also different tests for response to aspirin assessment.

Similar to our study, Iudici et al.[30] reported significantly lower CV problems in aspirin recipients than in non-aspirin recipients; therefore, they concluded that low-dose aspirin (100 mg/day) was a secure

therapy and might be useful in CV problems prevention in SLE cases. In the only study examining the pattern of low-dose aspirin consumption in RA cases with great CAD vulnerability based on a FRS ≥ 10%, underutilization of aspirin was confirmed mainly due to the perception that this is an issue which should be managed by the primary care physician.[10] About 19%-25% of people use low-dose aspirin in order to prevent from heart problems.[31] RA-related inflammatory signs are treated with aspirin and other NSAIDs.[32] Taking into account the higher risk of CAD in people with RA than in general people, it seems clear to use aspirin for treating patients with RA in order to prevent from CAD. The main mechanism of aspirin against thrombosis is inhibiting the COX-1 irreversibly, and therefore, inhibition of platelet TxA2 synthesis and consequently suppression of platelet reactivity.[11] There is also possibility that aspirin may lower the risk of CAD through its action as an antioxidant agent. Salicylate inhibits gene expression of nitric oxide synthase-2 (NOS2),[33] thereby lowers the nitrosative stress. Also, aspirin exerts antioxidant function on proteins and removes hydroxyl free radicals.[32]

Similar to our results, previous studies showed that Tx was not a target of disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate and hydroxychlroquine.[34,35]

The limitation of our study was the small number of participants. Further studies that expose a large number of patients with RA to aspirin and measure adherence to therapy will be required in order to characterize responses to aspirin in patients with RA. The strengths of our project included evaluating patients with RA in a setting presentative of routine clinical care and matched control participants.

Conclusion

Low-dose aspirin decreased sTxB2 level and suppressed platelet aggregation and therefore, was effective in primary prevention of CV events in patients with RA; however, additional studies are required to reach accurate conclusions.

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Authors' Contribution

Mehrzad Hajialilo designed the study, collected data, and helped in writing manuscript; Amir Ghorbanihaghjo helped in designing the study and performed biochemical measurements; Forough Ghassemi and Alireza Khabbazi helped in collecting data; Aida Malek-Mahdavi performed statistical analysis and wrote the manuscript.

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Conflict of Interest

Authors have no conflict of interest.

Ethical Approval

This study was accepted by the Ethics Committee of Tabriz University of Medical Sciences with the code of IR.TBZMED.REC.1395.638.

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