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ORIGINAL ARTICLE

Effect of Antiplatelet Activity of Aspirin on Chronic Kidney Disease

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ABSTRACT

Background and aim: Individual differences in the pharmacological responsiveness to aspirin are considerable. A higher likelihood of ischemic episodes is linked to aspirin's inadequate antiplatelet actions. It has been hypothesized that chronic kidney disease (CKD) influences the pharmacologic reaction to antiplatelet drugs. The elevated chance of fatality and cardiovascular problems in CKD sufferers has already been found to be largely explained by high on-treatment platelets response (HTPR) to clopidogrel. This research aimed to examine at how aspirin affects blood clotting in CKD sufferers.

Method: We performed cross-sectional research on 120 people in Medical center of Lahore taking aspirin regularly. The thromboxane production generated by AAI was used to gauge the pharmacologic reaction to aspirin.

Result: Individuals with poor kidney functioning were more likely to experience HTPR to aspirin (48% vs. 23%; odds ratio, 3.17; 95% confidence interval [CI], 1.35-7.42; P = 0.007). When compared to individuals with healthy or mildly diminished kidney performance, those with mild or serious CKD had lower pharmacokinetic responsiveness to aspirin (91; interquartile ranged [IQR], 281 ng mL-1; differential in medians, 56; CI, 6-110 ng mL-1; P = 0.012).

Remaining thromboxane production and glomerular filtration rate were both associated by bivariate Pearson correlation analysis (R = 0.312; R^2 = 0.093; P = 0.001). Individuals with CKD were usually old age and being women. Women and aged were not significant predictors of the connection, according to multivariate linear regression analyses (R = 0.313; R^2 = 0.081; P = 0.002 and P = 0.006) respectively.

Conclusion: Aspirin pharmacological reaction is associated with kidney function. Individuals who have CKD are more likely to have aspirin's antiplatelet action compromised. To evaluate the therapeutic significance of this data and look into the best antithrombotic strategy for CKD individuals, additional research is required.

Keywords: Chronic kidney disease, platelets, treatment, aspirin, cardiovascular

INTRODUCTION

The distinctive, un-expense cornerstone of chronic cardiac preventing diseases is antiplatelet therapy with acetylsalicylic activity (aspirin)[1]. Nevertheless, aspirin pharmacological reaction differs significantly between people [2]. High on-treatment platelet reaction (HTPR; also called "resistance") is the term used to describe inadequate antiplatelet actions. In individuals with coronary artery disease, adding HTPR to antiplatelet therapy is linked to higher fatality and implant thrombus occurrence [3]. When cerebrovascular events occur, aspirin's pharmacological reaction is weak, which worsens the brain hemorrhage[4]. Numerous variables have been identified as causing HTPR to aspirin, including decreased enteral uptake[5], biological causes [6], continuous aggravation [7], non-compliance [8], including co-medication with analgesics [9-10].

Over 600 million individuals globally are expected to suffer from some type of renal damage, making chronic kidney disease (CKD) a widespread global medical issue. According to study results, the CKD incidence grew in the American States from 15% to 18% between 1990 and 1998 and from 2000 to 2007 to 24% in 2015[2-4]. The epidemic of CKD is on the rise, with comorbid disorders like acute kidney injury playing a significant role. Subsequently, underpinning CKD is a primary health factor for both acute kidney damage and end-stage kidney diseases. According to reports, persons aged 70 and older are more likely to have phase 3 or phase 4 CKD than people aged 20 to 39, who are less likely to have it.

Importantly, multiple epidemiology research has revealed that, compared to the overall populace, patients who have CKD at all phases have increased frequencies of atherothrombotic illnesses and thromboembolic-probable mechanisms, including such atrial fibrillation[7,8]. This emphasizes how crucial antithrombotic treatment plans are for these individuals. Nevertheless, CKD may change the hazard-to-effectiveness ratio of antithrombotic medications. In addition, people with CKD are more likely to experience problems from bleeding [11,12]. Significantly, bleeding has become a standalone indicator of unfavorable results, especially death [14,15]. Individuals who have severe CKD are also less prone to be prescribed drugs that are effective[16]. These results, taken together, help to understand why individuals with diminished kidney function have a worse outcome than those with intact kidney dysfunction.

According to the International Renal Foundation, CKD is defined as either renal disease or a reduced renal glomerular filter rate. (GFR) of 60 mL • min1 • 1.75m2 for three months. A diagnosis of phase 1 and phase 2 CKD requires the presence of signs of structurally or functioning renal disease in addition to GFR, such as anomalies in blood, urination, or diagnostic imaging. Phases 3 through 5 are distinguished by gradients of GFR ranges. According to a US administration concept, end-stage renal illness covers all patients receiving hemodialysis or transplanted, irrespective of GFR[21]. Following table 1 is an overview of the various CKD phases.

Table 1: CKD stages

Stages of chronic kidney disease		
Stage	GFR	Description
I	≥90	Damage of the kidney with normal or elevated GFR
II	60-89	Damage of the kidney with a mild decrease in GFR
III	30-59	Moderate decrease GFR
IV	15-29	Severe decrease GFR
V	<15	Kidney failure

Aspirin acetylates cyclooxygenase-1 in a specific and irreversible manner, inhibiting the production of thromboxane A2 in platelets [17]. Although aspirin is primarily removed by liver processing, it can also be little and to varying degrees discharged unaltered in urine, depending on dosing and urinary pH. Kidney blood circulation in CKD patients must be maintained through prostaglandin-induced vasodilatation[18]. Aspirin increases the risk of additional renal dysfunction in CKD sufferers by preventing the formation of kidney prostaglandins. The packaging description advises against aspirin use in people with serious renal failure due to the aforementioned factors[19]. Whereas this advice is taken for preventive care, aspirin is still utilized in medical treatment in individuals with coronary artery disease symptoms despite the condition of extreme renal impairment. Apart from aspirin and acetaminophen, nonsteroidal anti-inflammatory medicines (NSAIDs) should have been avoided by patients with chronic kidney disease (CKD) due to further reductions in kidney blood flow capacity brought on by reduced prostaglandin production and, less commonly, intermittent interstitial nephritis.

Abnormal kidney performance is linked to higher fatality and more cardiovascular incidents occurring [12]. It is well reported that individuals with chronic kidney disease (CKD) [13,14] frequently

experience inadequate P2Y12 suppression by clopidogrel. These were considered to contribute to an adverse result in CKD individuals with coronary arterial diseases, amongst many other things [19]. In this research, we put out the hypothesis that HTPR to aspirin is linked to CKD. Hence, our goal was to examine the pharmacologic effects of aspirin in CKD sufferers.

METHODOLOGY

This research study design was cross-sectional at the Medical center for Kidneys in Lahore, 120 patients were one after the other while they were in the hospitalization stay. Aged over 18, written permission, and a daily intake of 100 mg of aspirin was required for inclusion. Confirmed thrombocytopenia and thrombocytopenia (under 100 000 L1) were the exclusionary criteria. Individuals were added one after the other. The National Kidney Foundation categorized kidney function [20].

Glomerular filtration rate (GFR) over 90 milliliters per min was used to describe CKD I (normal renal function), GFR from 60 and 89 milliliters per min was used to characterize CKD II (slightly impaired kidney function), GFR from 30 and 59 milliliters per min was used to describe CKD III, and GFR under 30 milliliters per min was used to describe CKD IV. The Modification of Diet in Renal Disease (MDRD) equation was used to determine GFR. The research received approval from the University and complied with the Declaration.

The function of platelet analysis: After aspirin was administered under supervision while the patient was hospitalized, platelet functional testing was performed. Venipuncture was utilized to take samples taken. A 21G needle has been used. Blood was drawn using suction tubes that were citrated (1:10). Before centrifuge, samples were kept at normal temperature for 15 minutes (1000 g for ten min). Before actual centrifugation, the precipitate was isolated and treated with arachidonic acid (AA) for five min (14 000 g for five min). The concentrations of thromboxane (TX) B2 in the supernatant were measured using an ELISA kit from Cayman Chemicals. This immunoassay is predicated on the rivalry involving TXB2 and a TXB2 pointer for a finite amount of specific receptors.

The amount of antiserum binding points covered by the TXB2 Tracer is inversely related to the amount of unbound TXB2 in the supernatant when the amount of the TXB2 pointer is kept fixed. So, a 96-well dish was filled with fifty L of the supernatant, fifty L of the TXB2 detector, and fifty L of the specific antibody. Monoclonal IgG that was earlier adhered to the dish wells attaches to the compound of rabbit monoclonal antibody and TXB2 (alone or TXB2 Pointer). The dish was rinsed to get rid of unattached chemicals after a 24-hour incubation period at 5 °C. Then an acetylcholinesterase substrate-containing reagent was administered. A spectrometer was used to gauge this catalytic reaction's final product's color strength. As was already noted, the quantity of unbound TXB2 in the probing is inversely linked to the quantity of attached TXB2 Pointer. The technique for measuring the pharmacodynamic reaction to aspirin [21] that we used was the AA-induced TXB2 production technique. TX serum concentrations exceeding 120 ng mL-1 were used to identify HTPR.

Statistical analyses: The sampling size was calculated using SPSS. A least of 108 patients were required to reach 90% statistical significance assuming linear regression 2-tail analysis, with α error of 0.05, an expected effect value of 0.1, and 3 variables. Aged and Body Mass index are shown as means with standard deviations, while TXB2 is shown as the median from n separate studies. P less than 0.05 was regarded as substantial. The Kolmogorov-Smirnov testing, histograms, and q-q plots were employed to examine the regularity of the data dispersion.

To test the homogeneity of variance, Levene's F-test was run out. There was no re-alignment of outliers had been used. The square root and logarithm transformation was inadequate, thus there was no data to be transformed. The t-test analysis was run to measure the data distribution normality and then a Mann-Whitney test was performed for the non-normality distribution of data. Also, the Pearson correlation and multiple regression analysis were run to analyze the correlation measurements. All these analyses were performed by using the statistical package for social science version 25.

RESULTS

Individuals were aged 70 to 15; 55% of them were men. Thirty-five patients had medium to severe CKD, while 85 patients had average or slightly decreased kidney function (45 patients with healthy kidney activity and 40 with mildly decreased renal performance) (twenty-seven patients with moderate CKD; eight patients with severe CKD). For the subsequent avoidance of cardiac disease, aspirin was a constant therapy for all patients. As a comparison to individuals with normal or minimally diminished kidney performance, individuals with moderate or severe CKD were just more probable to be women (75% vs. 38%, P 0.001). Individuals with normal or somewhat diminished kidney function also had a younger age (75±15 vs. 80±10 years, P = 0.035). Both categories shared similar cardiac risk factors and co-medication.

Table 2: Characteristics of patients

	Stage 1/2	Stage 3/5	P value
Age	70±15	80±10	0.035
Male	63 (55%)	15 (27%)	<0.001
Cardiovascular factor	75(92%)	33(99%)	0.105
Diabetes	21(23%)	34(100%)	0.104
Hypertension	16 (17%)	8 (19%)	0.924
Smoking			
Medication			
Aspirin	85 (99%)	33 (99%)	-
Ca channel	33(42%)	12 (42%)	1.000
inhibitor	55 (84%)	21 (62%)	0.497
Statin			

Pharmacokinetic response to medication, aspirin: When compared to individuals with normal or mildly diminished renal functioning, individuals with moderate to severe CKD had altered aspirin's antiplatelet actions as determined by TX formation (35 [101] nanograms per milliliter vs. 91 [281] nanograms per milliliter; variation in medians, 56; 95% interval of confidence [CI]; P = 0.011). As a result, individuals with impaired renal activity were more likely to experience HTPR (20 individuals [23%] in CKD stage 1 and 2 vs. 17 individuals [48%] in CKD stage 3 and 4; odds ratio, 3.17; CI, 1.35-7.42; p = 0.007).

When comparison with individuals of normal kidney performance, CKD 1, 25 (48 ng mL-1; n=43), the pharmacological responsiveness to aspirin was decrease in individuals with mild CKD 2, 72 (131 nanograms per milliliter; n=41); there is a differentiation in median, (47; CI, 6-68 nanograms per milliliter; p=0.002), moderate CKD 3, 75 (262 nanograms per milliliter; n=29); there is a differentiation in median, (51; CI, 4-157 nanograms per milliliter; p=0.0042), and severe CKD 4, 151 (263 nanograms per milliliter; n=7); there is a differentiation in median, (129; CI, 66-281 nanograms per milliliter; p=0.001).

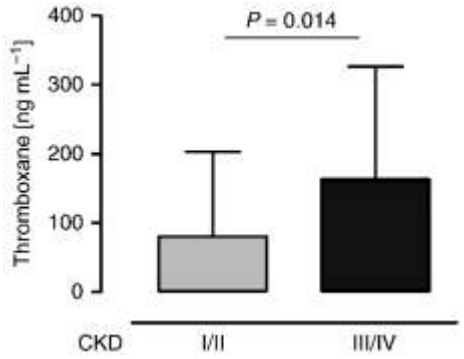

Figure 1:

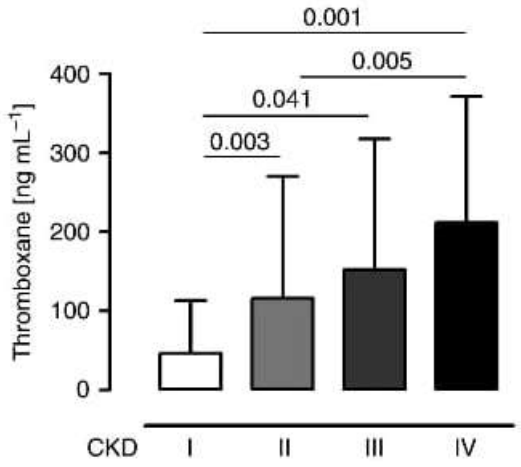

Figure 2:

Moreover, despite the therapy with aspirin, TX production was elevated in individuals with CKD 4, 151 (261 nanograms per milliliter) compared with individuals with CKD 2, 71 (131 nanograms per milliliter); there is a median difference, (80; CI, 0-223 nanograms per milliliter; p= 0.005). Lastly, there is a tendency for aspirin's antiplatelet actions to be more effective in individuals with mild kidney dysfunction than those with substantial damage CKD 2, 70 (131 nanograms per milliliter) vs CKD 3, 73 (260 nanograms per milliliter); a median difference of (4; CI-25-80 nanograms per milliliter; p=0.63), particularly in people who have mild kidney impairment as opposed to extreme renal failure CKD 3, 73 (260 nanograms per milliliter) vs CKD 4, 150 (261 nanograms per milliliter); a median difference of (77; CI-96-178 nanograms per milliliter; p=0.20) had been seen as well. Bivariate Pearson correlation analyses revealed a negative correlation between platelet TX production and glomerular filtrate rate ($R = 0.312$; $R^2 = 0.093$; $P = 0.001$). Aged ($R = 0.313$; $R^2 = 0.081$; $P = 0.002$) and sexuality ($R = 0.30$; $R^2 = 0.07$; $P = 0.006$) had no effect upon it.

Table 3:

Predictor	R	R^2	Adjust R^2	Beta	p value
GFR	-0.312	0.093	0.083	-0.302	0.001
GFR, sex	-0.30	0.07	0.076	-0.286	0.006
GFR, age	-0.313	0.081	0.081	-0.290	0.002
GFR, age; sex	-0.316	0.098	0.074	-0.276	0.007

DISCUSSION

The primary conclusions of this research included HTPR to aspirin is related to the degree of CKD, and residual TX generation is related to kidney dysfunction as assessed by GFR for individuals having aspirin therapy.

In individuals taking aspirin, CKD is linked to an increased risk of mortality and coronary events[22]. This poor result has been attributed to a variety of factors, such as increased arterial stiffening and calcified [22], endothelial impairment [23], systemic inflammation [24], anemic, and left ventricle enlargement [25]. Furthermore, several investigations have revealed that HTPR to clopidogrel is more common in CKD individuals [14–17] and is linked to a worse result [20].

Tanri et al. identified a greater probability of HTPR in individuals with CKD [25] of the antiplatelet impacts of aspirin and the condition. In comparison, in the Brett et al. study [23] overall was no reduction in aspirin's antiplatelet impacts after controlling for confounders. Additionally, Gremmel et al. reported a greater frequency of HTPR to aspirin when assessed using the platelet tester but not when assessed using optical transmitted aggregometry [15]. As AA-induced TX production is the most precise technique for assessing the antiplatelet actions of aspirin [21], we thus evaluated it in this investigation.

In this investigation, we discovered that aspirin had no discernible positive effects on CKD patients. Aspirin usage, on the other hand, was linked to this negative outcome and a higher incidence of cardiovascular events in those individuals. Additionally, these negative impacts have no impact on CVE's initial prevention. With a higher bleeding chance, the antiplatelet treatment showed little to no impact on lowering cardiovascular severity and fatality in CKD individuals. In a prior study, it was found that taking low doses of aspirin raised the risk of cardiovascular disease and kidney advancement, indicating that aspirin is detrimental for people with kidney disease. These results supported the conclusions of the present investigation. Aspirin medication did not significantly lower the risk of cerebral attack, cardiovascular death, or all-cause death in patients with severe CKD on predialysis, according to a new study conducted across the country in individuals with CKD G5. Additionally, the study demonstrated a link between aspirin use and a higher risk of renal dysfunction in those individuals. These results further confirm the harmful effects of aspirin therapy on CKD individuals.

Patients receiving antiplatelet drugs for subsequent preventive have been shown to have a greater incidence of CVE and death when there is inadequate antiplatelet efficacy, also referred to as the high on-treatment platelet responsiveness (HTPR)[26]. It has recently been demonstrated that people with CKD experience HTPR more frequently than do those with appropriate renal function [23-25]. In other words, diminished kidney function reduces the impact of antiplatelet medications.

We were capable of showing that aspirin's diminished antiplatelet actions are correlated with kidney dysfunction as determined by GFR. This could be because CKD sufferers' platelets have higher levels of von Willebrand factors, active glycoprotein IIb/IIIa activity, and thrombin production [26]. There is also a rise in the number of platelets tiny particulates having procoagulant action. It is well established that aspirin's diminished antiplatelet actions are linked to increased fatality[27]. HTPR to aspirin may indeed increase the risk of cardiovascular incidents and patient mortality. There are currently no clinical studies comparing individuals with and without CKD to determine if aspirin is less effective in preventing cardiac ailment in individuals with CKD. Experimental studies are required to evaluate this extremely pertinent subject, bringing the pharmacological findings of this investigation into consideration.

There are a few restrictions on this research. Because it is a pharmacokinetic trial, clinical results could not be predicted. The cohort under investigation was heterogeneous and hence reflected an actual population. The association between GFR and thromboxane production has a poor R2 rating. This wasn't shocking, yet, as TX production measurements of the inter-individual reaction to aspirin are well known to have significant inter-individual variation. Due to the cross-sectional nature of the investigation, platelet responsiveness before the start of aspirin administration wasn't examined. There were no time-series studies done as the CKD progressed. A significantly high probability of ischemia episodes exists in dialysis individuals with end-stage kidney impairment. Blood exposed to the hemodialysis membranes is reported to significantly improve platelet responsiveness [28]. If these individuals are comparable to CKD individuals without hemodialysis, platelet responsiveness may be significantly greater, irrespective of aspirin medication. The current research has not looked into this. Additional research is hence required to evaluate this extremely pertinent subject.

CONCLUSION

In conclusion, aspirin's antiplatelet actions and renal health are connected. A decreased pharmacokinetic responsiveness to aspirin is linked to CKD. This could explain why CKD patients have a higher occurrence of cardiovascular problems. When giving aspirin to individuals with persistent renal impairment to avoid

cardiac events, it must be done so individually. Massive trials are required to examine how this pharmacologic result affects the clinical result and the most effective antithrombotic regimen in sufferers with chronic kidney disease.

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