International Journal of Natural Medicine and Health Sciences
ISSN (Online):2790-2471 ISSN(Print): 2790-2463
Volume 1, No.2, March 2022
Journal homepage: https://journals.iub.edu.pk/index.php/ijnms

Original Research

Role of Aldose Reductase in Ischemic Heart Disease in Subjects Visiting Punjab Institute of Cardiology, Lahore

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Article Info.

Received: 06-03-2022
Revised: 24-03-2022
Accepted:26 -03-2022
Online: 30-03-2022

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Keywords: Ischemic heart disease, aldose reductase, total glucose, total cholesterol, high-density lipoprotein

Abstract

Background: Ischemic heart disease (IHD) is one of the major cardiovascular diseases due to insufficient blood supply to cardiac cells. Aldose reductase (AR) is a multifunctional enzyme that converts glucose into sorbitol in the polyol pathway. The main objective of this study is to determine the role of aldose reductase in ischemic heart disease subjects in our local population and its relationship with lipid profile. Methods: This cross-sectional study sampled 100 subjects from Jelani Block of PIC Lahore after ethical approval, categorized into two groups depending on disease condition, i.e., the IHD (n=50) group and Control Group (n=50), including healthy subjects. They were taken together with disease history, age, smoking, hypertension, and physical activity examined as inclusion criteria. The level of biochemical parameters was evaluated by using a chemistry analyzer. Hormonal (AR) and cardiac marker (CK-MB) assessments were performed on the ELISA system using commercially available ELSA diagnostic kits. Results: The results revealed that levels of aldose reeducate and CK-MB was comparatively more significant in the IHD group than control, but total cholesterol (TC), triglycerides (TG), and high-density lipoproteins (HDL) showed no significant difference between the control and IHD group. Conclusion: A statistically non-significant relationship was observed between aldose reductase and CK-MB and lipid profile in the IHD patients, indicating the role of aldose reductase in IHD subjects because it increases oxidative stress in cardiac cells.

Citation: Sharif S, Saleem A, Abbas MK, Saeed L, Mustafa W, Prince K, Lan F, Role of Aldose Reductase in Ischemic Heart Disease in Subjects Visiting Punjab Institute of Cardiology, Lahore. IJNMS. 2022; 1(2): 75-81.

Introduction

Ischemic Heart Disease belongs to a group of cardiovascular diseases. Coronary heart disease includes angina (stable and unstable), sudden coronary death, and myocardial infarction; coronary atherosclerosis is the primary factor for IHD [1,2]. The initial development of coronary artery diseases is mainly due to atheromatous plaque formation. In early atheroma formation, pro-inflammatory cytokines promote the development of atherosclerosis [3].

Many factors are associated with IHD like obesity, diabetes, high blood pressure, malnutrition, smoking, lack of exercise, excessive alcohol intake, and depression [4]. A high level of circulating aldose reductase is associated with increased atherosclerosis, and a low level has a protective effect on tissues and cells [5]. Now IHD has become a leading cause of health problems in developed and underdeveloped countries, causing equal mortality in both genders. Every year, nearly 500,000 deaths are associated with IHD. Coronary Artery Disease (CAD) decreased in developed countries between 1980 and 2010 [6].

Aldose Reductase belongs to the Aldo-keto reductase family. AR is the aldehyde-metabolizing enzyme that catalyzes the glucose to sorbitol conversion; it is the first step in glucose metabolism [7]. AR triggers the accumulation of sorbitol and oxidative stress that causes osmotic pressure on cells due to NADPH/NADP+ and NAD+/NADH concentration changes that may enhance several diabetes complications [8].

Conversion of glucose to sorbitol occurs by the Aldose Reductase gene (ALR2) under the hyperglycemic conditions in the polyol pathway. Sorbitol accumulation causes cataracts, microvascular complications, increased osmotic and oxidative stresses, and cardiac ischemic injury. AR mediates cardiac ischemic injury in both diabetic and non-diabetic animals. [9]. Aldose reductase increases atherosclerosis formation in the arteries. Ischemic conditions increase AR flux. Its inhibition reduces vascular injury [5]. Increased activity of aldose reductase was studied under ischemia-reperfusion conditions (I/R). An enhanced polyol flux pathway contributes to raising the injury in the myocardium. Studies implicate AR act as a chief player in the progression of I/R damage in the heart [10]. Improved Cardiac functions were also observed in aldose reductase inhibited nature to ischemic injury [11].

Creatinine kinase (CK-MB) release marker was significantly lower in aldose reductase inhibited subjects. However, the difference in the CK-MB level is observed after stroke. CK-MB is more sensitive and gradually elevated during myocardial injury. CK-MB correlated better with aldose reductase (AR) than any other parameter [12]. Among all risk factors, total cholesterol is treated as the critical risk factor for IHD. Plaque formation is observed due to changes in arteries present in children and adults [13]. Metabolic syndromes increase the risk of coronary artery disease by 7.3times in males and 10.2 times in female patients [14]. Globally, IHD became the most common cause of mortality from 2012 to 2015 resulting in 422.7 million prevalent cases of CVD in 2015 110.55 million cases of IHD [15]. Similarly, IHD is one of the prominent causes of death in many parts of Karachi, Pakistan. About 16 % population below 45 years of age are suffering from IHD.

The current study was designed to examine the role of AR in causing cardiovascular diseases and its association with lipid profile.

Materials and methods

The present cross-sectional study was executed at the Punjab Institute of Cardiology, Lahore, from January to July 2015. After approval from the hospital's ethical committee and LCWU, data was collected from Jelani Block and the hospital's emergency department. A total number of 100 subjects were sampled during this study.

The study population was categorized into two major groups, the IHD group (n=50) and the control group (n=50). The subjects diagnosed by the physician who were suffering from IHD were enrolled in the study. Demographic data regarding disease history, smoking, physical activity, and all risk factors were obtained through a self-designed questionnaire. Height and weight were determined; BMI was calculated using the formula (Kg)/height m^2. Blood pressure was measured, and fasting blood samples were collected to measure lipid profiles (TC, TG, and HDL) analyzed by the chemistry analyzer urite-800. Serum aldose reductase and CK-MB were analyzed using commercially available ELISA diagnostic kits at the ELISA system [15].

Statistical analysis:

All datasheet was prepared on MS excel 2010. Data were evaluated as mean ± SEM. The normal distribution of data was checked separately through the Shapiro Wilk test, which showed data skewness. The difference between normally distributed data between groups was found with the help of the T-test. The correlation of CK-MB with AR and lipid profile was evaluated through the Bivariate Pearson correlation. The significance level was based on the 0.05 probability level, and the highly significant level was based on a 0.01 probability level at a 95% confidence interval. The exclusion criterion was strictly followed to minimize the effects of confounding factors. The statistical analysis was performed by the SPSS version [16].

Results

A total of 100subjectswere enrolled and sampled. Comparison of age, BMI, systolic, diastolic blood pressure, TC, TG, HDL, CK-MB, and AR were shown in Table 1. Among Ischemic heart disease patients (n=50), 30% were females, 70% were males, 32% were male, and 68% were females in the control group. The frequency with and without physical activity among IHD subjects was higher than in the control group. It was observed that the percentage of smokers (50%) was more in IHD patients than in control subjects (20%).

The analysis revealed that the mean age values (61.36 ± 1.14 years) of IHD patients and healthy subjects (62.5 ± 1.47 years) were not statistically different. Systolic blood pressure and total cholesterol were elevated in the IHD group compared to the control group.

Table 1 shows a highly significant difference in mean values of CK-MB in the IHD and control groups. Systolic blood pressure total cholesterol also showed a significant difference between the groups. On the other hand, the percentages of subjects with no physical activity and previous IHD history were higher in the disease group.

To further explore the association between ischemic disease and aldose reductase in IHD, the association was found by Bivariate Pearson Correlation presented in table 2. Bivariate correlation analysis of AR with TC, HDL, TG, and CK-MB in IHD and control showed no significant relationship of AR with lipid profile and cardiac enzyme.

Discussion

Myocardial damage is due to the death of cardiac cells due to ischemia which is the most common cause is atherosclerosis. Hypertension, diabetes, age, high lipid profile, gender, and smoking are the most common risk factors for atherosclerosis. Males are commonly at increased risk of IHD at a younger age than females. Coronary disease affects the South Asian population relatively early than Western people [17].

According to the World Health Organization (WHO), reports that approximately22.2% of men and 2.1% of women do tobacco smoking in Pakistan. Generally, 100 million people die worldwide every year due to diseases caused and spread by tobacco use. It is estimated that by 2030, one in every six persons will die due to the severe effects of smoking. Roughly expected that among these deaths, 50% of subjects belonged to the middle-age group (35-69years) [18]. Teo et al.2018 stated that there are 1.3 billion smokers estimated worldwide. Most Asian people spend their money on alcohol and smoking instead of on education and a healthy diet, which causes adverse effects on the cardiac system [19]. Previous studies showed that physical activity has a beneficial impact in Ischemic Heart Disease. People with cardiac artery diseases can be better by aerobic exercise like jogging, swimming, and walking [20]. The amount of blood cholesterol (LDL) and blood pressure is decreased by aerobic exercise over time. Aerobic exercise also enhances the HDL cholesterol, known as "good cholesterol [21]. This study showed a similar result to our present study, in which we observed that the %age of patients has a low vigorous exercise in the IHD subjects compared to the control group. Many other studies also revealed that IHD and physical activity have a strong relationship.

Since there is no special diet and medication available to increase HDL levels, the best dietary approach to improve and convert the total cholesterol or LDL to HDL is substituting monounsaturated fats for carbohydrates [16]. Our study found that with the increase in cholesterol concentration, the risk for IHD also increases and becomes more evident in both sexes. It has been found that total cholesterol is a significant risk factor for IHD, as in blood pressure and smoking [32, 33]. It has been suggested that the decrease in egg consumption lowers cholesterol concentration and IHD risk. Many studies showed that serum cholesterol concentration increases by dietary cholesterol intake. At the end of this study, total cholesterol (TC) mean values were higher in the IHD patients than in the control group, and these groups showed a highly significant difference. The population in Japan with a low cholesterol concentration has a much lower IHD mortality rate than the Western populations [23]. Previous studies [24] indicated that the incidence of cardiac events amplified with increasing serum total cholesterol values, which are according to our studies as illustrated in Tables 1 and 2.

CK-MB is a sensitive and specific biomarker for myocardial infarction. CK-MB begins to raise its level 4-6 hours after myocardial damage, at an extreme level within 24 hours, and then returns to normal values in 48-72 hours. CK-MB estimated level helps diagnose cardiac injury and the diagnosis of myocardial infarction [17]. The present study showed that patients with a high level of CK-KMB are at a higher risk of cardiac diseases. Mehta P. K, et al. 2014 showed that the release of these two crucial enzymes, CK-MB and Troponin-1, is related to Myocardial infarction. The elevated level of CK-MB may be a factor for myocardial damage in the Q-wave that is linked with the formation of Q-wave in ECG [4].CK-MB was found to be a better indication of Acute Myocardial Infarction (AMI), and in the initial hours, its sensitivity is more significant than any other biomarker in IHD. CK-MB has a very short half-life in IHD patients. High CK-MB level in the IHD patients indicates myocardial damage like coronary artery blockage or stenosis that leads to the CK-MB release from cardiac monocytes. CK-MB shows a strong correlation with total cholesterol.

Our study found that cardiac disease in Pakistani patients rises due to some risk factors such as smoking, high blood pressure, unhealthy diet, and physical inactivity. In this study, we designed experiments to evaluate the role of aldose reductase in the progression of IHD. Azab et al. conducted research and concluded that lipid profile is the significant predictor of mortality in IHD patients; our study was also following the results of these previous studies. In the present study, the level of aldose reductase was observed to be high in IHD patients compared to the control group. Many risk factors related to disease development are studied, such as smoking, physical activity, diabetes, and lipid profile. We found that aldose reductase also plays an essential role in the progression of IHD by converting glucose into sorbitol in the polyol pathway and osmotic, oxidative stresses, cardiac ischemic injury, cataract, and microvascular problems that lead to the sorbitol accumulation. The previous showed that sorbitol accumulation could increase oxidative stress, microvascular damage, and myocardial ischemic heart injury [23]. During this study, we also assessed the correlation of AR with CK-MB and lipid profile (TG, TC, and HDLC). There is no significant relationship exists between aldose reductase and CK-MB. Oxidative and osmotic stress is characterized by an increase in the generation of reactive oxygen species. It was found that the increased level of lipids in IHD subjects has increased due to the production of reactive oxygen species in the hyperglycemic state [25].

In this study, the relationship of aldose reductase with triglycerides (TG) was also studied, and it showed no significant correlation in the control and IHD groups with TG. Results of the present study showed similarity with the study of (Schrijvers B.F. et al. 2004: Naghavi M., et al. 2003), who observed that increased level of CK-MB in patients who have ischemic stroke causes acute coronary syndromes [3, 9]. The relationship of aldose reductase with CK-MB was not substantial. The mean values of aldose reductase and CK-MB significantly

differed CK-MB values exceeded the acute myocardial infarction.

Conclusion

The level of AR was higher in patients diagnosed with IHD than in healthy subjects. Diet, smoking, age, and lipid profile were other most prominent traditional risk factors among IHD patients. It was evident from this study that a highly significant difference exists between mean values of CK-MB in the control and IHD groups. The study also found a correlation between AR and cardiac marker (CK-MB), indicating no significant association. AR plays a central role in biochemical and molecular stress that characterizes the pathogenesis of cardiovascular diseases. AR physiological actions are still open to debate. However, a few limitations regarding the small number of enrolled subjects: more well-designed studies are needed to investigate the role of AR in IHD subjects.

Conflict of interest

The authors declare no conflict of interest regarding this paper.

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Table 1. Biochemical and demographic parameters of control and IHD groups.

Variables	Control group(n=50)			IHD group(n=50)		
	All	Male	Female	All	Male	Female
Age (Years)	62.52 ± 1.47	63.11 ± 1.77	61.11 ± 2.74	61.36 ± 1.14	62.5 ± 1.36	58.66 ± 2.03
BMI (Kg/m^2)	24.22 ± 0.66	23.86 ± 0.96	25.36 ± 0.54	25.11 ± 0.39	23.82 ± 0.4	23.08 ± 0.94
Systolic (mmHg)	122.0±1.5*	121.7 ± 2.14	122.5± 1.3	129.9±2.54*	126.6± 2.7	137.6 ± 5.3
Diastolic (mmHg)	85.44±2.40	83.58 ± 2.16	89.3 ± 5.03	81.90 ± 1.40	81.9 ± 1.4	85.66 ± 2.48
TC (mg/dl)	170.63±7.9**	170.5±5.4**	170.9 ± 10.8	200.29±5.9**	206.08± 7.6**	187.11± 7.9
TG (mg/dl)	148.7±13.7	132.8±12.29	182.32±32.5	181.48±13.2	194.4±17.6	151.1 ± 13.8
HDLC (mg/dl)	12.79±0.21	12.93±0.22	12.45±0.42	34.36±4.30	31.89±3.64	40.29±6.35
CK-MB(U/L)	6.44 ± 2.75	6.17 ± 0.6	11.00 ± 7.00	83.4±49.01**	80.7 ± 7.7	89.66±14.85
AR (pg/ml)	202.64±18.51	1.97 ± 26.29	2.12 ± 26.17	239.99±18.67	2.30 ± 20.55	2.61 ± 40.36

*: between the groups the significant difference is ($p \leq 0.05$)

**: between the groups the highly significant difference is ($p \leq 0.01$)

Table 2. Correlation of AR with other risk factors.

Variables	Control Group (n=50)	IHD Group (n=50)
TC (mg/dl)	0.16	-0.12
TG (mg/dl)	0.004	-0.12
HDLc (mg/dl)	-0.34	-0.24
CK-MB (U/L)	0.06	-0.13

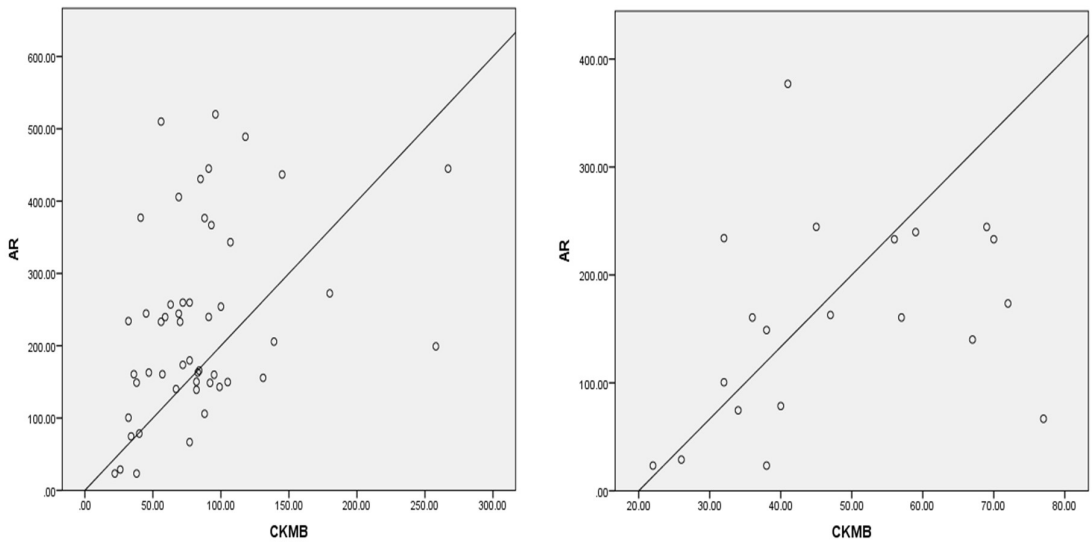

Fig: 1: Scattered plot showing a correlation between AR (pg/dl) and the CK-MB (U/L) in diabetic and Non-Diabetic subjects in the IHD group respectively.

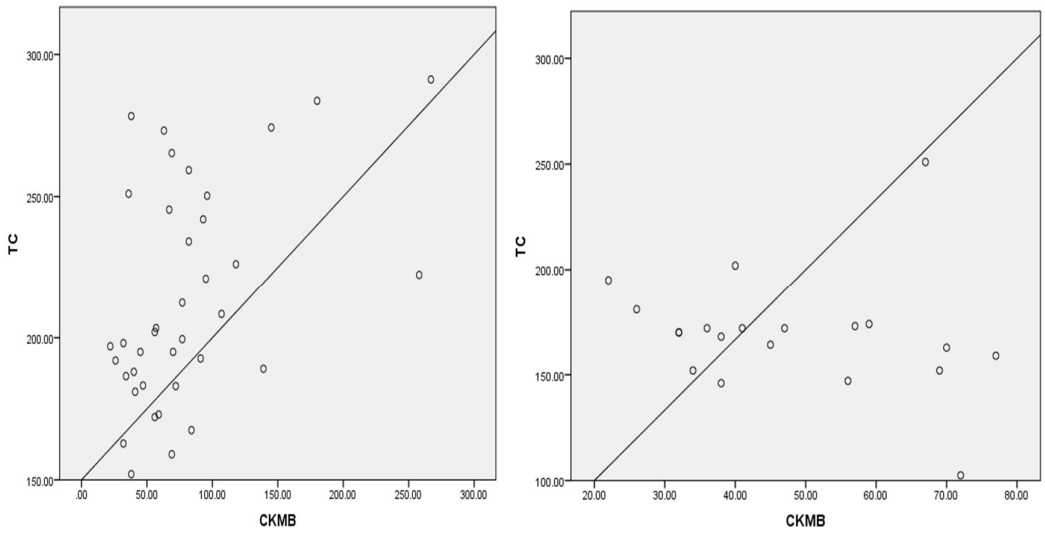

Figure 2: Scattered plot showing a correlation between TC (mg/dl) and CK-MB (U/L) in Diabetic and Non-Diabetic subjects in the IHD group respectively.