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Original Article

Anti-Atherosclerotic Effects of Pioglitazon by Interference with Inflammatory and Stress Pathway in Male Rabbits

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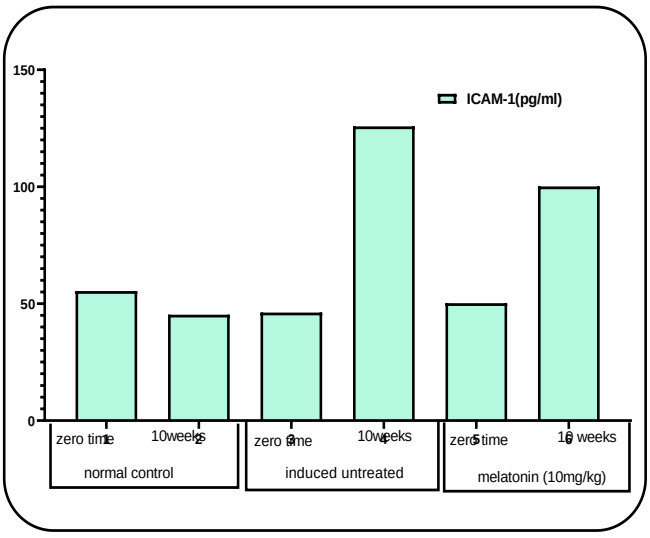
ABSTRACT

Atherosclerosis is the leading cause of death worldwide. It is now widely accepted that it is a chronic inflammatory process. Minor inflammation, increased oxidative stress, and lipid peroxidation are all the important factors in the cancer pathogenesis. Pioglitazone is an oral diabetes medication that belongs to the thiazolidinedione's pharmacological class, a medication that acts on the peroxisome proliferator-activated receptor (PPAR). Therefore, the PPAR activation prevented coronary artery disease as a result of pioglitazone, anti-inflammatory effects, and arteriosclerosis down-regulation of CCR2 in circulating monocytes. The aim of this research is to asses if pioglitazone can protect rabbits against atherosclerosis. Twenty-four domestic male rabbit were divided into three groups; Group I, normal control group (no = 8), Group II (no = 8): Rabbits fed a cholesterol diet (the induced untreated group). Group III (no = 8): 1% cholesterol l diet oral pioglitazone 3 mg/kg once day before breakfast. Animals fed an atherogenic diet had the lower levels of GSH, SOD, and higher levels of total cholesterol, triglycerid, HDL-C, LDL-C, VLDL-C, atherogenic index, iCAM, and intimal thickness compared with controls ($P < 0.001$). In comparison to the induced untreated group, pioglitazone has a significant impact on lipid parameters ($P < 0.001$). Pioglitazone significantly reduced the elevation in ICAM, and a mild effect on the aorta thickness compared with induced the untreated groups ($p < 0.05$). The drug resort the aortic GSH and SOD level ($P < 0.001$).

GRAPHICAL ABSTRACT



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Introduction

Atherosclerosis is regarded as a persistent inflammatory reaction of the wall of arteries irresponse to dyslipidemia combined with endothelial disturbance involving the inflammatory recruitment of leukocytes with the activation of local vascular cell [1]. The persistent inflammation of arterial vascular wall is considered to produce multifocal plaque development. Plaque is a sticky substance comprised of fat, cholesterol, calcium, and other things [2]. As plaque builds up, the arteries become rigid and narrow acute and chronic lumina blockage, irregular blood flow, and reduced oxygen availability to target organs are all possible outcomes [3].

Many inflammatory mediators have been identified as having an impact on the progression of atherosclerotic plaques. CD40L produced within the plaque, for example, has been found to boost tissue factor expression in atherosclerotic plaques. The smooth cells within the atherosclerotic plaque produce various inflammatory mediators, including interleukin (IL)-1ß, tumor necrosis factor (TNF), IL-6, M-CSF, MCP-1, IL-18, IL-17A, and CD-40L, among others [4].

The acute phase reactants such as C-reactive protein (CRP), tumor necrosis factor (TNF), interleukin-6 (IL-6), serum amyloid A, and fibrinogen are among the most significant inflammatory markers because they provide an indirect measure of the cytokine-dependent inflammatory process in the artery wall [5].

CRP may play a direct role in the atherosclerosis etiology, according to research. CRP is highly up-regulated in atheromatous plaques, where it may increase LDL-C uptake by macrophages, a critical stage in atherogenesis, according endothelial cells may also express the intercellular adhesion molecules, which may facilitate the recruitment of circulating monocytes to plaque locations. In addition, the C-reactive protein can bind and activate complement in serum, which may result in an inflammation increase. These effects appear to be mediated via Endothelin-1 and IL-6 release produced by CRP [6]. Antioxidants are any chemical (molecule, compound, or enzyme) that has a substantial antioxidant effect. The majority of antioxidants are electron donors, which combine with free radicals to produce harmless end products like water. As a result, antioxidants protect cells from oxidative stress and damage. Antioxidants come in various forms [7].

TNF- interferes with GSH production through a variety of pathways, resulting in reduced GSH levels. TNF-alpha production is also increased by the oxidative stress. As a result of the GSH disruptions and increased TNF-alpha production/activation, a pathogenic loop or vicious cycle is developed [8, 9].

Pioglitazone is an antihyperglycaemic agent (thiazolidinedione-type) that improves hepatic and peripheral insulin sensitivity in the presence of insulin resistance, inhibiting hepatic gluconeogenesis and increasing peripheral and splanchnic glucose uptake. Pioglitazone is generally well tolerated. There are no known drug interactions, and no known emergent adverse events in interaction between pioglitazone and other medications pioglitazone can used as mono-therapy or in a combination with metformin, repaglinide, insulin resistance, or a sulfonylurea, all induced both long- and short-term insulin resistance [10].

Improvements in glycemic control and serum lipid profiles happen in the short-term. In addition, pioglitazone was effective at lowering certain measures of cardiovascular risk and arteriosclerosis. Thus, pioglitazone represents an effective treatment option for management of type 2 diabetes patients (Table 1) [11].

Pioglitazone increases whole-body adiposity by boosting lipid storage and redistribution from visceral to subcutaneous deposits, as well as adipocyte differentiation. It further appears to have antihypertensive, atherosclerosis, and antihypertensive actions [12].

Materials and Methods

24 domestic male rabbits from the surrounding area were divided into three groups;

Group I normal Control group (n = 8).

Group II (n = 8): Rabbits fed a 1% cholesterol diet (induced untreated group).

Group III (n = 8): 1% cholesterol diet + oral pioglitazone 3 mg/kg once day before breakfast. Blood samples were taken before (0 time) and after every 2 weeks of atherogenic meals to test blood triglycerides (TG), total cholesterol (TC), HDL-C, VLDL-C, and ICAM. The aorta was excised after 10 weeks to evaluate aortic SOD, reduced glutathione (GSH), and aortic intimal thickness. The typical rabbit diet was comprised of 10% wheat, 40% grass powder, 13% soybean cake, 20% maize, 10% wheat bran, 3% fish flour, 1% salt, 3% bone meal, and 1% multivitamins (percent by weight).

Results and Discussion

There was a significant change in the body weight of pioglitazone receiving group and induced untreated group, while an insignificant change was observed in body weight of pioglitazone receiving group and normal group. There was a significant difference in serum levels of TC, TG, LDL, and VLDL-C between the normal control group (I) and the groups on an atherogenic diet (II and III), and there were significant differences in the serum level of induced untreated group (II) and pioglitazone treated group (III). The baseline values of serum ICAM were not statistically significant in any of the groups prior to the trial (Table 2, Figure 1). The ICAM levels in the induced untreated group significantly were raised after 2 weeks of atherogenic diet. After 8 weeks, the ICAM level was significantly increased compared with zero time. After 10 weeks, the serum ICAM levels of the pioglitazone treated groups were considerably (P<0.001) lower than those of the induced untreated group (II). The treated groups had significantly greater aortic GSH levels than the induced untreated group (II). Pioglitazone (III) treated group had significantly higher aortic SOD levels after 10 weeks than the induced untreated group (II). Also, a significant improvement (P >0.001) was observed in atherosclerosis histological intima thickness (Table 3, Figure 2, 3).

Table 1: Serum lipid profile (TC, TG, and HDL) by using paired T- test

		TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)
Control Normal (I)	Zero time	28.37±3.28	88.7±2.04	20.20±0.72
	10 weeks	44.63±3.93	75.41±8.44	17.05±3.23
Induced untreated (II)	Zero time	44.64±8.25	78.36±6.89	24.8±4.61
	10 weeks	1026.38±14.83	451.7±14.3*	33.3±5.23*
Pioglitazone group (III)	Zero time	47.87±5.15	77.61±4.32	14.62±2.37
	10 weeks	447.37±15.39*	429.1±14.27*	43.14±6.0*

**p<0.001*

Table 2: Serum levels of inflammatory marker ICAM in rabbit by using paired T-test

		ICAM-1(pg/ml)
Control normal (I)	Zero time	55.4±2.34
	10 weeks	70.50±3.84
Induced untreated (II)	Zero time	73.2±3.21
	10 weeks	125.8±1.67**
Pioglitazone group (III) 3 mg/kg	Zero time	63.2±4.21
	10 weeks	105.2±2.97**

P<0.001

Table 3: Average values of SOD and GSH for aortic oxidative stress by using paired T-test

	Aortic GSH (ng/l) aorta	Aortic SOD (pg/ml) aorta
Control normal (I)	23.36 ± 1.76	330.4±27.20
Induced untreated (II)	15.23 ± 1.43*	180.1±23.92*
Pioglitazone group (III)	20.95 ± 2.10**	276.6±19.03**

***P<0.05, as compared with normal control, *P<0.05, as compared with induced untreated*

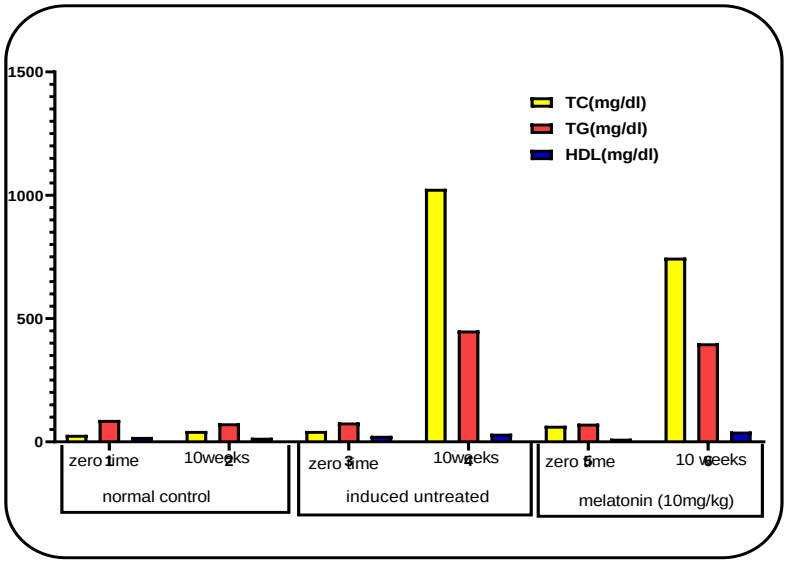

Figure 1: Effect of pioglitazone on the serum level of TC, TG, and HDL

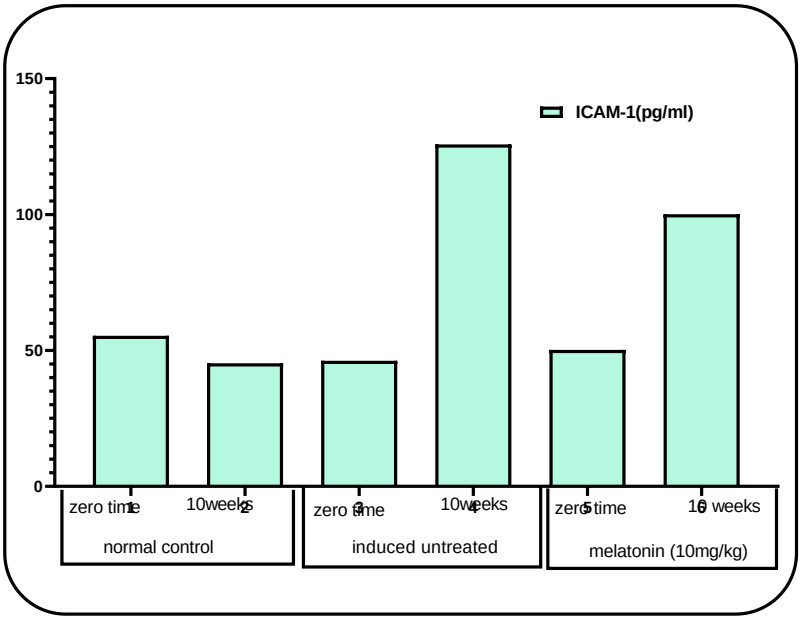

Figure 2: Comparison between the group and effect of pioglitazone on ICAM level

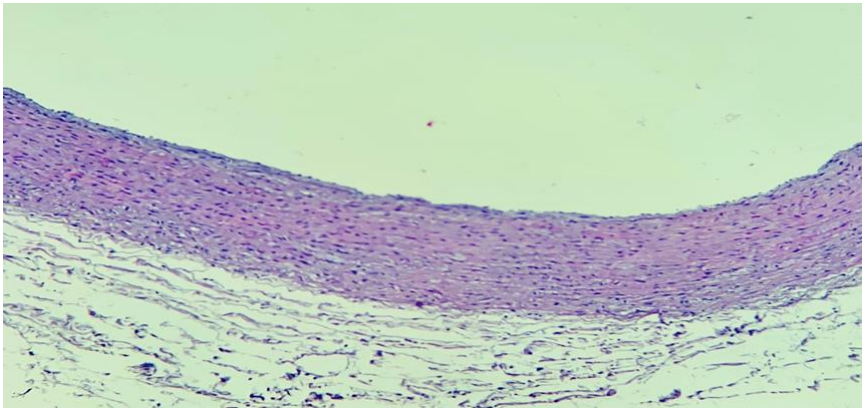

Figure 3: The formation of arterial wall layers in aortic arch of rabbits feed normal diet

A common and serious complication of type two diabetes is accelerated atherosclerosis, which is accompanied by a high-risk of premature mortality from cardiovascular disease (such as coronary heart disease) [13]. Therefore, it is essential for the management of individuals with this entity to avoid the onset, or development of atherosclerosis, and to maintain the appropriate glycemic control. The goal of the current study was to evaluate how pioglitazone affected oxidative and inflammatory pathways to treat atherosclerosis. Our findings showed that eating a high-cholesterol diet for 10 weeks, increased all serum cholesterol profile part and accelerated the development of atherosclerotic lesions, such as the intima thickening and/or accumulation of lipid droplets beneath endothelial cells in the carotid artery. In addition, the findings of the current study demonstrated that pioglitazone treatment could dramatically reduce ICAM-1 and other inflammatory markers, which were shown to be much greater in atherosclerotic rabbits. This particular study shows that treatment with pioglitazone appeared to have a significant effect on lipid parameters when compared with the induced un-treated group.

The findings of this investigation are consistent with Bahriz *et al.* (2021) and Ishii (2022) who had discovered that there was a considerable change in lipid characteristics in rabbits that had been given cholesterol, and then treated with pioglitazone, and this may be due to that pioglitazone decreases the cholesterol levels through improving the cholesterol clearance from the circulation. This is most likely accomplished by an increase in lipoprotein lipase-mediated lipolysis, and treatment with pioglitazone for an extended period of time resulted in sustained improvements in both triglyceride and HDL-C levels (Figures 4, 5) [14].

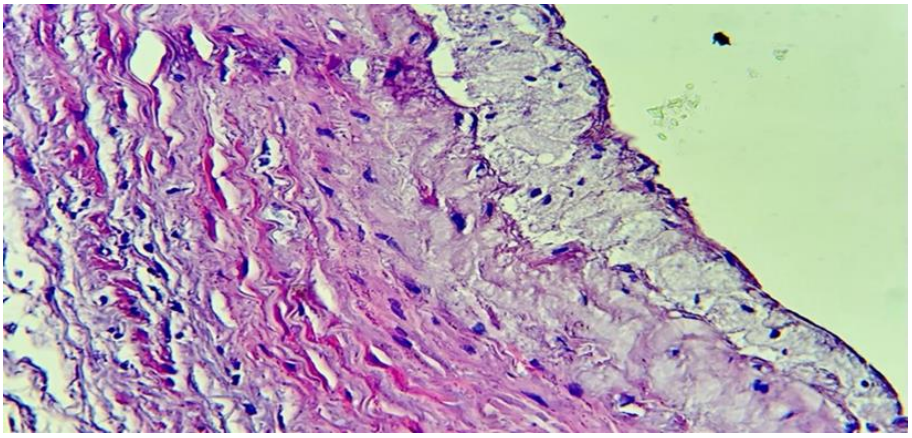

Figure 4: The formation of arterial wall layers in aortic arch of rabbits feed atherogenic diet for 10 weeks

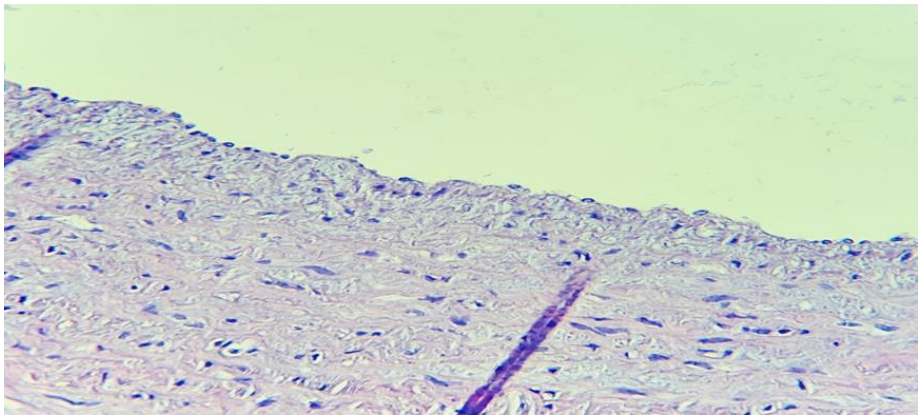

Figure 5: The formation of arterial wall layers in aortic arch of rabbits feed pioglitazone hyperlipidemia for 10 weeks

This investigation was agree with Liang *et al.* (2021)and Shah and Rathi (2022) which indicate pioglitazone have a considerable effect on lipid profiles and glucose homeostasis because of the stimulating effect they have on peroxisome proliferator-activated receptor gamm (PPAR) receptors. Meanwhile, pioglitazone has the potential to drastically reduce TG levels while simultaneously raising the HDL levels.

It is possible that the anti-inflammatory properties of pioglitazone were responsible for preventing coronary arteriosclerosis. Pioglitazone has been shown to have anti-inflammatory and anti-arteriosclerotic properties, which may be mediated by the drug's ability to down regulate the CCR2 expression in circulating and lesion monocytes. Pioglitazone may have the unique anti-inflammatory effects through inhibiting the CCR2-mediated inflammation [15, 16].

Aortic SOD level was dramatically decreased by pioglitazone indicating a reduction in ROS and the ensuing lipid peroxidation. In hyper-cholesterolemic rabbits, pioglitazone also had a significant impact on the aortic GSH levels, preventing GSH depletion and maintaining the antioxidant reserve necessary for vascular protection against lipid peroxide and pioglitazone consistently caused a considerable drop in the Aortic LPO (lipid peroxide test) level [17].

Pioglitazone significantly reduce the tissue MDA level in diabetic rat [18], and it may have the ability to up-regulate the genes for antioxidant enzymes including PON1, SOD, and CAT by inhibiting the nuclear factor kappa-B (NF-B), which is redox sensitive [19, 20]. Another explanation for pioglitazone's antioxidant capability is that it possesses agonistic properties for the PPAR receptor [21, 22].

In this work, pioglitazone was reported to dramatically decrease the elevation of inflammatory markers (ICAM) in a hyper-cholesterolemic rabbit atherosclerosis model which suggests that pioglitazone inhibits the vascular inflammation caused by a high-cholesterol diet. This finding was made possible by the fact that the rabbits were fed a high-cholesterol diet [23-28].

Conclusion

The findings of the current study suggest that pioglitazone may reduce the evolution of atherosclerosis in hyper-cholesterolemic rabbits by interfering with inflammatory and oxidative pathways and influencing lipid parameters.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

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