

Assessment of Anti-Atherosclerotic Activity of Aminoguanidine on Diabetes Accelerated Atherosclerosis

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Abstract This research is designed to assess the anti-atherogenic activity of aminoguanidine against diabetes-accelerated atherosclerosis in albino rats. The Wistar albino rats (150-200 g) were used for the investigation. Animals were fed an atherogenic diet for 45 days after by acute intraperitoneal injection of alloxan (120 mg/kg) on the 0th day. From day 16th to 45th, group II (atherogenic control) received normal saline (10 ml/kg/day, p.o.), group III (standard) received atorvastatin (10 mg/kg/day, p.o.), group IV (aminoguanidine-25) received intraperitoneal injections of aminoguanidine at a dose 25 mg/kg/day, and group V (aminoguanidine-50) received intraperitoneal injections of aminoguanidine at a dose 50 mg/kg/day. The results showed the potential beneficial effect on aminoguanidine-treated animals especially at 50 mg/kg dose level, when compared to the atherogenic control group. Aminoguanidine treatments significantly restore the body weight, serum lipid levels (total cholesterol, triglycerides, LDL, VLDL, and HDL), atherogenic index, and serum hepatic biomarkers (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphate). Moreover, results showed the potent antioxidant activity of aminoguanidine, which is indicated by significant restoration in hepatic oxidative stress markers like catalase, reduced glutathione, malonaldehyde, and nitrite content in the aminoguanidine treatment group. Overall results conclude that aminoguanidine mitigates the

progression of atherosclerosis against diabetes-accelerated atherosclerotic animal model by its potent antihyperlipidemic and antiatherogenic activity.

Keywords Aminoguanidine, Diabetes, Atherosclerosis, Alloxan, High-Fat Diet

1. Introduction

Cardiovascular diseases and diabetes are the most common causes of morbidity and mortality in now a day. According to epidemiological research, hyperlipidemia, and diabetes mellitus (DM), are considerably induced by improper diet management, which is the prominent risk factor for DM, hyperlipidemia, and cardiovascular disease (CVD). It is well known that atherosclerosis exacerbates rapidly and early in those with DM compared to people without DM, and persons with DM are far more likely to acquire CVD [1]. In patients with DM, CVD is the most prevalent cause of mortality. In the United States, CVD death rates are 1.7 times more prone in adults (over 18 years of age) with DM compared to those without DM, mainly due to increased risk of stroke and myocardial infarction [2]. Fifty to seventy percent of individuals with

diabetes mellitus (DM) also experience CVD. Complications from diabetes are closely related to how high blood sugar levels rise and how they remain elevated. Both type 1 and type 2 DM contribute to faster development of arteriosclerosis [3].

DM is majorly classified into type-1 and type-2 DM. Autoimmune destruction of pancreatic β -cells is the major cause of type-1 DM. Therefore, production of insulin is defective in these patients [4]. However, type-2 DM often develops over the time with obesity. Insulin resistance is major health risk in patients with DM and involve in hepatic, muscles, and adipose tissues [5]. Insulin exhibits variety of biological activity by activating the insulin receptor including glycogen and lipid synthesis. In the insulin resistance condition, action of insulin is impaired and suboptimal in target tissues. Insulin resistance exacerbates the pathophysiological conditions of metabolic disorders [6]. Insulin resistance can lead to atherosclerosis *via* variety of mechanisms like deregulation in lipid metabolism, endothelial dysfunction, and vascular dysfunction [7].

Atherosclerosis is a long-term inflammation of the artery walls. This condition often results in serious disability or even death. On the other hand, diabetes is a complicated disorder affecting carbohydrate metabolism. It usually goes hand in hand with high sugar levels. This happens due to two main reasons: insufficient insulin production, poor insulin function, or sometimes both. Insulin plays a key role as an anabolic hormone, and when it's lacking, it leads to various metabolic issues in proteins, lipids, & carbohydrates [8]. Atherosclerosis develops through multiple stages and can eventually result in cardiovascular disease, which has a significant impact on mortality rates. The changes in lipid metabolism are both a risk factor for atherosclerosis and a characteristic of it. Many studies have explored the possible connections between chronic diseases like these by looking at shifts in metabolic pathways [9]. DM exacerbates the progression of atherosclerosis at almost every stage of the atherogenic process by hyperglycemia, dyslipidemia, and other metabolic changes accompanying disease development are closely involved in atherosclerosis pathogenesis [10]. Chronic inflammation plays a crucial role in the development of atherosclerosis, which is closely related to DM. But here's the thing: we still don't have solid data on how to create effective anti-inflammatory treatments to stop or even reduce those awful atherosclerotic lesions. Therefore, it is postulated that anti-inflammatory drugs may be helpful to reduce the progression of diabetic-induced atherosclerosis [11]. In this area, aminoguanidine stands out. It exhibits potent antiglycation activity [12], anti-inflammatory activity [13], and anti-oxidant activity [14]. So, in this study, we evaluated the anti-atherosclerotic activity of aminoguanidine on diabetes-accelerated atherosclerosis.

2. Materials and Methods

2.1. Chemicals

Alloxan monohydrate (Loba Chemie Pvt. Ltd, Mumbai, India), and aminoguanidine (Sigma-Aldrich Chemicals Pvt. Ltd. Bangalore, India) were procured from Chemical suppliers, Bilaspur, CG, India. Diagnostic kits for Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), plasma alkaline phosphate (ALP), total Cholesterol (TC), triglycerides (TG), and high-density lipoprotein (HDL) were procured from Beacon Diagnostics Pvt. Ltd, India. All other analytical grade chemicals and reagents were procured from the departmental chemical store.

2.2. Experimental Animals and Diets

We used male healthy Wistar albino rats (150-200 g) for the investigation. Experimental animals were procured from Chakraborty Enterprises, 3/1D Girish Vidyaratna Lane, Narkeldanga, Kolkata-700011. After that, they were kept in the departmental animal house facility for experimental purposes under hygienic conditions ($25^{\circ}\text{C} \pm 2$, 55% RH, 12-12 hours light-dark cycle). Before the experiment started, the rats in the animal facility were given at least seven days for acclimatization. The Committee for Control and Supervision of Experimental Animals (CPCSEA) under reference number 256/IAEC/Pharmacy/2018 and the Institutional Animal Ethics Committee of the Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur (Reg No-994/GO/Re/S/06/CPCSEA), have approved the studies and methods presented in this paper.

Thirty rats in all were picked at random and placed into five groups, each with six rats. The rats in Group I were fed a regular diet and served as a normal group. In groups II to V, diabetes was induced by acute intraperitoneal injection of alloxan (120 mg/kg) on the 0th day. Thereafter, an atherogenic diet of 40% sugar, 10% butter, 1 % sodium cholate, and 2% cholesterol (w/w) was fed to the rats in Groups II to V for the next 45 days. From day 16th to 45th, group II (atherogenic control) received normal saline (10 ml/kg/day, p.o.), group III (standard) received atorvastatin (10 mg/kg/day, p.o.), group IV (aminoguanidine-25) received intraperitoneal injections of aminoguanidine at a dose 25 mg/kg/day, and group V (aminoguanidine-50) received intraperitoneal injections of aminoguanidine at a dose 50 mg/kg/day [15].

After completion of the experimental protocol, animals were kept overnight fasting and then sacrificed under an overdose of anesthesia. The liver tissues were isolated right away and then dried using filter paper after being washed with an ice-cold saline solution. The liver was ground into a 10% particle size using a 7.4 pH 0.1M phosphate buffer solution. After a heart puncture procedure, blood was extracted and placed in tubes with citrate buffer [16].

2.3. Biochemical Analysis

Twenty-four hours following the last scheduled dose, the animals received an intraperitoneal dose of 60 mg/kg of ketamine and 10 mg/kg of xylazine, a moderate aesthetic. The retro-orbital plexus was then punctured using a capillary tube to collect blood. One to two ml of blood was drawn into each Eppendorf tube for every animal in each group. The drawn blood was cold-centrifuged at 2000 rpm for 20 minutes after being left for 30 to 45 minutes to aid in coagulation. The serum supernatant was evaluated for turbidity after being transferred to an additional Eppendorf tube. The combination is subjected to a further centrifugation procedure if turbidity is detected, which lasts for 10 minutes at a speed of 2000 revolutions per minute. The technique made use of a distinct serum sample, and biochemical markers such as AST, ALT, ALP, TC, TG, LDL, and HDL levels were examined using diagnostic kits. Very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and atherogenic index (AI) were calculated by using a formula [17].

$$\text{VLDL} = \text{Triglyceride}/5$$

$$\text{LDL} = \text{TC} - (\text{HDL} + \text{VLDL})$$

$$\text{AI} = \text{TC} - \text{HDL}/\text{HDL}$$

Oxidative stress markers were measured in the supernatant of the liver tissue homogenate. Catalase (CAT) activity was estimated by the methods of Aebi, [18]. Superoxide dismutase (SOD) activity was observed by using the method of Kakkar et al. [19]. Reduced glutathione (GSH) was monitored by using the method of Ellman et al. as described by Goyal and Anil [20, 21]. Malondialdehyde (MDA) was estimated by assessing thiobarbituric acid reactive substances (TBARS) by the method of Goyal and Anil [21]. Nitrite content was determined by the procedure described by Guevara et al [22].

2.4. Statistical Analysis

The mean \pm standard error of the mean (SEM) was used to express the presented values. The statistical study employed an analysis of variance (ANOVA). The computations were performed using the statistical software Graph Pad Prism. In every study, a corresponding $P < 0.05$ was considered significant.

3. Results

3.1. Effects on Body Weight

Results on body weight are presented in Figure 1. When compared to the normal group (group I), group II showed a significant ($P < 0.05$) increase in body weight. When compared to Group II (atherogenic control group), groups III, IV, and V showed a significant ($P < 0.05$) decrease in body weight from day 35 to day 45.

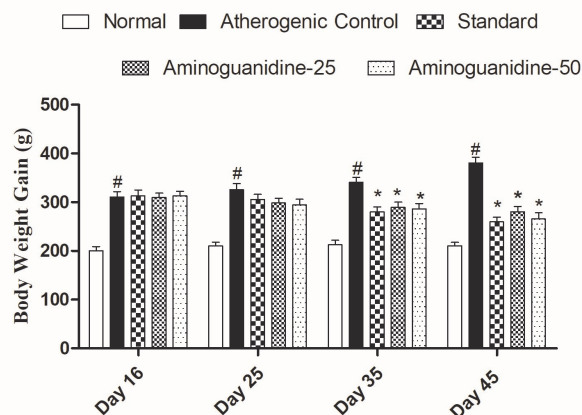


Figure 1. Effect of Aminoguanidine on body weight on atherosclerotic diabetic rats. Values are expressed as mean \pm SEM (n=6), and statistical evaluation was carried out using a two-way analysis of variances followed by Bonferroni's post hoc test. # $P < 0.05$ when compared to the normal group and * $P < 0.05$ when compared to the atherogenic control group

3.2. Effects on Lipid Profile and Atherogenic Index

Results on lipid profile are presented in Table 1. In the atherogenic control groups, when compared to the normal group, a significant ($P < 0.05$) increase in serum TC, TG, LDL, and VLDL levels, and a decrease in HDL level were observed. Whereas, in standard and aminoguanidine-treated groups, when compared to the atherogenic control group, a significant ($P < 0.05$) improvement in serum TC, TG, LDL, VLDL, and HDL levels was observed. Moreover, results (Figure 2) also indicated a significant ($P < 0.05$) improvement in the atherogenic index after treatment with atorvastatin and aminoguanidine treatments in their respective groups.

Table 1. Effect of Aminoguanidine on lipid profile on atherosclerotic diabetic rats

GROUP	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
Normal	140.4 \pm 6.66	143.3 \pm 7.08	28.33 \pm 1.62	83.37 \pm 8.07	28.67 \pm 1.41
Atherogenic Control	332.2 \pm 11.17#	312.5 \pm 15.59#	12.67 \pm 0.88#	257.1 \pm 10.98#	62.50 \pm 3.11#
Standard	205.2 \pm 12.21*	175.3 \pm 7.64*	22.17 \pm 1.64*	148.0 \pm 12.48*	35.03 \pm 1.53*
Aminoguanidine-25	243.2 \pm 9.96*	213.0 \pm 9.51*	20.17 \pm 1.30*	180.4 \pm 11.15*	42.60 \pm 1.90*
Aminoguanidine-50	224.5 \pm 11.03*	183.0 \pm 9.35*	21.67 \pm 2.07*	166.2 \pm 12.97*	36.60 \pm 1.87*

Values are expressed as mean \pm SEM (n=6), and statistical evaluation was carried out using a one-way analysis of variances followed by Tukey's post hoc test. # $P < 0.05$ when compared to the normal group and * $P < 0.05$ when compared to the atherogenic control group.

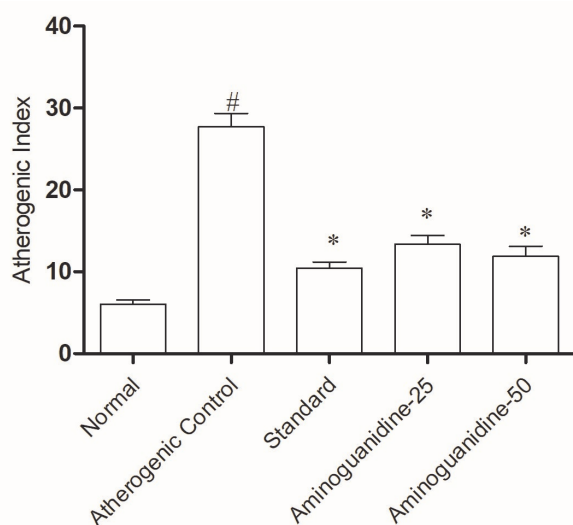


Figure 2. Effect of aminoguanidine on atherogenic index. Values are expressed as mean \pm SEM (n=6), and statistical evaluation was carried out using a one-way analysis of variances followed by Tukey's post hoc test. [#] $P < 0.05$ when compared to the normal group and ^{*} $P < 0.05$ when compared to the atherogenic control group

3.3. Effects on Serum Hepatic Biomarkers

Results on serum hepatic biomarkers like ALT, AST, and ALP are presented in Table 2. When compared to the normal control group, the atherogenic control group showed significant ($P < 0.05$) elevation in serum hepatic biomarkers like ALT, AST, and ALP. However, when compared to the atherogenic control group, atorvastatin and aminoguanidine treatment groups significantly ($P < 0.05$) reduced such serum hepatic biomarkers.

3.4. Effects on Hepatic Oxidative Stress Biomarkers

The antioxidant activity was assessed on liver tissues and results are presented in Table 3. When compared to the normal control group, the atherogenic control group showed a significant ($P < 0.05$) reduction in CAT activity and GSH level, and an elevation in MDA and nitrite levels, which were significantly ($P < 0.05$ vs the atherogenic control group) restored by treatments of atorvastatin and aminoguanidine in their respective groups.

Table 2. Effect of Aminoguanidine on hepatic biomarkers on atherosclerotic diabetic rats

GROUP	ALT (U/L)	ALP (U/L)	AST (U/L)
Normal	20.02 \pm 1.54	53.75 \pm 3.17	26.18 \pm 2.34
Atherogenic Control	46.33 \pm 2.64 [#]	157.8 \pm 3.95 [#]	70.18 \pm 2.08 [#]
Standard	24.60 \pm 1.23 [*]	73.0 \pm 2.86 [*]	32.76 \pm 1.53 [*]
Aminoguanidine-25	30.22 \pm 2.07 [*]	103.7 \pm 3.01 [*]	41.72 \pm 2.22 [*]
Aminoguanidine-50	26.72 \pm 1.92 [*]	90.50 \pm 3.49 [*]	36.65 \pm 1.46 [*]

Values are expressed as mean \pm SEM (n=6), and statistical evaluation was carried out using a one-way analysis of variances followed by Tukey's post hoc test. [#] $P < 0.05$ when compared to the normal group and ^{*} $P < 0.05$ when compared to the atherogenic control group.

Table 3. Effect of Aminoguanidine on hepatic oxidative stress biomarkers

GROUP	SOD (U/g)	MDA (nmoles/g)	CAT (μ moles H ₂ O ₂ consumed/mg/min)	GSH (μ moles/g)	Nitrite (nmoles/g)
Normal	66.17 \pm 5.19	60.0 \pm 2.28	78.43 \pm 2.83	16.0 \pm 0.57	10.50 \pm 0.76
Atherogenic Control	25.33 \pm 1.74 [#]	131.70 \pm 3.25 [#]	24.50 \pm 2.20 [#]	3.5 \pm 0.45 [#]	29.83 \pm 1.24 [#]
Standard	44.83 \pm 2.57 [*]	75.17 \pm 2.70 [*]	61.0 \pm 5.82 [*]	11.22 \pm 0.83 [*]	16.50 \pm 0.99 [*]
Aminoguanidine-25	35.83 \pm 2.75 [*]	93.0 \pm 2.33 [*]	42.0 \pm 2.88 [*]	8.35 \pm 0.55 [*]	19.50 \pm 1.33 [*]
Aminoguanidine-50	41.33 \pm 2.26 [*]	71.50 \pm 2.81 [*]	55.67 \pm 3.70 [*]	10.90 \pm 0.79 [*]	17.0 \pm 1.03 [*]

Values are expressed as mean \pm SEM (n=6), and statistical evaluation was carried out using a one-way analysis of variances followed by Tukey's post hoc test. [#] $P < 0.05$ when compared to the normal group and ^{*} $P < 0.05$ when compared to the atherogenic control group.

4. Discussion

Type-2 DM is strongly associated with Hyperlipidaemia and disturbed liver functions, which further exacerbates atherosclerosis [23, 24]. The present study demonstrated the potential beneficial effects of aminoguanidine treatments against diabetes-accelerated atherosclerosis. In the present study, atherosclerosis was induced by acute administration of alloxan along with chronic feeding of a high-fat diet. Results of the present study show that aminoguanidine considerably reduced the body weight, when compared to the atherogenic control group, indicating it has a potential beneficial effect on body weight.

It is well established that monitoring of lipid profile helps to assume the dyslipidemia/hyperlipidemia conditions. In the hyperlipidemia conditions, TC, TG, LDL, and VLDL levels increase and HDL level decreases in serum [25, 26], which was observed in the atherogenic control group when compared to the normal group. Whereas serum lipid profile was significantly restored by treatments of aminoguanidine indicating the anti-hyperlipidemic effects of aminoguanidine. Results also indicate that aminoguanidine at 50 mg/kg had better anti-hyperlipidemic effects.

The literature explained that higher levels of TC, TG, LDL, and lower levels of HDL are strongly related to an augmented risk of atherosclerosis and CVD [27, 28]. The anti-atherosclerotic activity was assessed in this study by monitoring AI. As we discussed above, diabetes and hyperlipidemia exacerbate atherosclerosis, which is presented by AI in the present study. The aminoguanidine treatment significantly reduced the AI, when compared to the atherogenic control group. The anti-atherosclerotic effects of aminoguanidine might be due to its potential anti-hyperlipidemic effects, because AI is related to the level of TC and HDL. Higher levels of TC and lower levels of HDL increase the AI which was observed in the atherogenic control group, while lower levels of TC and higher levels of HDL decrease the AI which was observed in the aminoguanidine-treated groups. The results also indicate that aminoguanidine at 50 mg/kg had better effects than at 25 mg/kg dose level.

A plethora of literature revealed that Advanced glycation endproducts (AGEs) are the major concern in the diabetes conditions. AGEs are generated when lipids and proteins are exposed to sugar and become glycated by non-enzymatic process and are accelerated in DM. Formation and accumulation of AGEs further lead to variety of cardiovascular pathophysiological events including oxidative stress, vascular damage, and atherosclerotic events. The acceleration of the development of atherosclerotic plaque is primarily by two mechanisms: either directly, by changing the extracellular matrix molecules in the artery wall's functional characteristics, or indirectly, by stimulating signaling pathways dependent on cell receptors [29]. In this study we

did not assess the role of AGEs but it is another important parameter to assess the diabetes-accelerated atherosclerosis.

Moreover, a plethora of literature demonstrates that diabetes and hyperlipidemia may cause hepatic damage [30, 31]. The serum ALT, AST, and ALP are, authentic hepatic biomarkers, elevated during liver damage condition [32]; which was observed in the atherogenic control group. Whereas, aminoguanidine treatment considerably reduced the serum hepatic biomarker against diabetic hyperlipidemia. These results indicate the hepatoprotective action of aminoguanidine, which might be due to the antioxidant properties of aminoguanidine.

It is well established that the antioxidant defense system of the biological system maintains the homeostasis between the reactive oxygen species and antioxidants, and further protects the cellular damages. The excessive production of reactive oxygen species and depletion of endogenous antioxidants like CAT and GSH are the characteristic features of oxidative stress [33, 34], which are studied in the present research. The kinds of literature also validates the strong relationship between diabetes, hyperlipidemia, and oxidative stress [35, 36]. Therefore, we assessed the oxidative stress markers in the liver tissues. The results showed potent antioxidant activity of aminoguanidine, which is indicated by significant restoration in oxidative stress markers like CAT, GSH, MDA, and nitrite content in the aminoguanidine treatment group.

5. Conclusions

Based on findings, aminoguanidine at 50 mg/kg/day dose level had considerable beneficial effects against atherogenic conditions. It significantly restored the body weight, lipid profile, hepatic biomarkers, and oxidative stress markers. Overall results conclude that aminoguanidine mitigates the progression of atherosclerosis against diabetes-accelerated atherosclerotic animal model by its potent antihyperlipidemic and antiatherogenic activity.

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Conflict of Interest Statement

We now declare that we do not possess any conflicts of interest.

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