Evaluation of the effects of glimepiride (Amaryl) and repaglinide (novoNorm) on atherosclerosis progression in high cholesterol-fed male rabbits

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ABSTRACT

Background: Atherosclerosis is an inflammatory disease of the blood vessel wall, characterized in early stages by endothelial dysfunction, recruitment and activation of monocyte/macrophages. Glimepiride is one of the third generation sulphonylurea drugs, useful for control of diabetes mellitus type two and it may exert anti inflammatory activity, by induction of nitric oxide production or through selective suppression of the cyclooxygenase pathway. Repaglinide is a new hypoglycemic agent, and a member of the carbamoylmethyl benzoic acid family. Some results from the literature demonstrate that repaglinide has favorable effects on the parameters of antioxidative balance. **Objectives:** The objective of the present study was to assess the effect of glimepiride and repaglinide on atherosclerosis via interfering with the inflammatory and oxidative pathways. **Materials and Methods:** Twenty four local domestic male rabbits were involved in this study. The animals were randomly divided into four groups; Group I rabbits fed normal chow (oxiod) diet for 10 weeks. Group II rabbits were fed with 1% cholesterol enriched diet. Group III rabbits were fed with 1% cholesterol enriched diet together with Glimepiride (0.1 mg/kg once daily before morning feed). Group IV rabbits were fed with 1% cholesterol enriched diet together with Repaglinide (0.3 mg/kg once daily before morning feed). Blood samples were collected before (0 time) and every two weeks of experimental diets for measurement of serum triglycerides (TG), total cholesterol (TC), High-density lipoprotein cholesterol (HDL-C), high sensitive C - reactive protein (hsCRP), Interleukin – 6 (IL-6) and Tumor Necrosis Factor alpha (TNF-α) levels. At the end of 10 weeks, the aorta was removed for measurement of aortic Malondialdehyde (MDA), reduced glutathione (GSH) and aortic intimal thickness. **Results:** Glimepiride and repaglinide treatment did show significant effect on lipid parameters compared with induced untreated group ($P < 0.05$). Also, they significantly reduced the elevation in hsCRP, IL-6, TNF-α, aortic MDA and aortic intimal thickness compared with induced untreated group ($P < 0.05$), and they helped to restore the aortic GSH levels ($P < 0.05$). **Conclusions:** Glimepiride and repaglinide may reduce atherosclerosis progression in hypercholesterolemic rabbits by interfering with the inflammatory and oxidative pathways without affecting lipid parameters.

Key words: Atherosclerosis, glimepiride, inflammatory markers, oxidative stress, repaglinide

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INTRODUCTION

A main consequence of type II diabetes is accelerated onset of atherosclerosis, which is an important risk factor in the progression of ischemic cardiovascular disease. Successful management of hyperglycemia alone is usually inadequate to prevent cardiovascular events, as many other recognized

risk factors such as hyperlipidimia, hypertension, and obesity are often present concurrently in the diabetic population.[1] Also the incidence of atherosclerosis is 3 – 4 times greater in diabetics than non-diabetics at comparable plasma total cholesterol concentrations.[2] Accordingly, prevention of onset and progression of atherosclerosis, as well as tight glycemic control are essential goals of treatment in type two diabetic patients. It has been extensively demonstrated that inflammation plays a central role in atherogenesis, and mediates all stages of this disease, from initiation through progression and, ultimately, the thrombotic complications of atherosclerosis.[3]

Inflammation contributes to the formation and progression of atherosclerosis, and the therapeutic potential of some anti-inflammatory drugs has been evaluated for possible anti atherosclerotic activity. Recent findings suggest that some agents with anti-inflammatory properties appear to have beneficial effects on atherosclerosis, or subsequent risk for cardiovascular events.[4] Sulfonylureas have been widely used in the recent years as a first-line treatment in type two diabetic patients in whom the blood glucose levels could not be effectively controlled by di*et al*.one. Glimepiride (Amaryl®), a third-generation sulfonylurea administered once daily, has been established to offer therapeutic advantages over other sulfonylureas in terms of glucose level-dependent insulinotropic action, insulin-sparing effects, and hypoglycemic risk.[5-7] Furthermore, glimepiride exhibits inhibitory effects on human platelets aggregation through selective suppression of the cyclooxygenase pathway, suggesting that it may have therapeutic potential in diabetic patients with enhanced platelet function.[8] In addition, there are several reports showing beneficial effects of sulfonylureas against the development of cardiovascular disease in rabbits fed an atherogenic diet,[9] as well as in hyperglycemic patients.[10] Recently, glimepiride has been demonstrated to inhibit the development of atheromatous plaques in the thoracic aorta of high-cholesterol fed rabbits.The mechanism by which glimepiride induces atheroprotective effects remains to be elucidated.[11]

Repaglinide is a new hypoglycemic agent, and a member of the carbamoylmethyl benzoic acid family. Its mechanism of action is partially similar to that of sulfonylurea. It stimulates the release of insulin from pancreatic beta-cells by inhibition of potassium efflux lead to closure of Adenosine triphosphate (ATP) regulated Potassium Ino (K+) channels.[12] This results in depolarization of the cell and subsequent opening of the calcium channels, leading to an influx of calcium into the cells, and causing release of insulin.[13] However, repaglinide regulates these channels via a different binding site than sulfonylurea. Repaglinide improves glycemic control through a physiological action on the reduced phase of insulin secretion in type 2 diabetes mellitus.[14] Some results from the literature demonstrate that repaglinide has a favorable effect on the parameters of antioxidative balance. It significantly improved the activity of superoxide dismutase and diminished lipid peroxidation in the serum of type 2 diabetic patients.[15] It is possible that the drug itself, being a benzoic acid derivative, has some antioxidant activity.[15]

MATERIALS AND METHODS

Twenty four local domestic male rabbits were involved in this study. The animals were randomly divided in to four groups; Group I rabbits fed normal chow (oxiod) diet for 10 weeks. Group II rabbits fed with 1% cholesterol enriched diet for 10 weeks. Group III rabbits fed with 1% cholesterol enriched diet together with glimepiride (0.1 mg/kg once daily before morning feed for 10 week).[16] The drug was prepared immediately before use as a suspension in 5% starch. Group IV rabbits were fed with 1% cholesterol enriched diet together with repaglinide (0.3 mg/kg once daily before morning feed for 10 week).[17] The drug was prepared immediately before use as a suspension in 5% starch. The blood samples were collected before (0 time) and every two weeks on experimental diets for measurement of serum triglycerides (TG), total cholesterol (TC), HDL-C, high sensitive C - reactive protein (hsCRP), IL-6 and TNF-α level. At the end of 10 weeks, the aorta was removed for measurement of aortic Malondialdehyde (MDA), reduced glutathione (GSH) and aortic intimal thickness.

RESULTS

There was a slight insignificant increase in the body weight of Glimepiride and Repaglinide receiving groups suggesting that food consumption probably was similar in all the groups and cholesterol or glimepiride or repaglinide had no effect on body weight. Also no significant changes were observed in the glucose concentration of the glimepiride and repaglinide receiving groups during the period of experiment. A significant increase was onserved in the blood glucose concentration levels of the induced untreated group, and this may be because an atherogenic diet reduces plasma insulin levels and enhances gluconeogenesis as shown in Table 1.

Compared with the control, levels of TC, TG, HDL-C, LDL-C, VLDL-C, atherogenic index, hsCRP, IL-

6, TNF-α, MDA and aortic intimal thickness were increased, and GSH were decreased in the animals on the atherogenic diet ($P<0.05$). Glimepiride and repaglinide treatment did not show any significant effect on the lipid parameters when compared with the induced untreated group ($P>0.05$). Glimepiride and repaglinide significantly reduced the elevation in hsCRP, IL-6, TNF-α, aortic MDA and aortic intimal thickness compared with induced untreated group ($P<0.05$). Also they restore aortic GSH level ($P<0.05$) as shown in Tables 2-5 and Figures 1-9.

Table 1: Changes of body weight (kg) and blood sugar (mg/dl) levels of the four experimental groups of rabbits. The data was expressed as Mean ± Standard error of mean (SEM) (N = 6 in each group) using paired T-test

		Body weight (Kg)	Blood sugar (mg/dl)
Normal control	Zero time	1.5 ± 0.1	110 ± 4.2
	10 weeks	1.5 ± 0.09	100 ± 6.2
Induced untreated	Zero time	1.55 ± 0.1	110 ± 6
	10 weeks	1.3 ± 0.05	134 ± 4*
Glimepiride 0.1 mg/kg	Zero time	1.52 ± 0.1	112 ± 5.2
	10 weeks	1.64 ± 0.05	124 ± 5.7
Repaglinide 0.3 mg/kg	Zero time	1.6 ± 0.07	107 ± 5.3
	10 weeks	1.73 ± 0.06	120 ± 6.8

**P< 0.05*

DISCUSSION

Accelerated atherosclerosis accompanied by high risk of premature mortality from cardiovascular disease (eg coronary heart disease) is a frequent and serious complication of type two diabetes.[18] Thus prevention of onset or progression of atherosclerosis, as well as adequate glycemic control is mandatory for the treatment of patients with this entity. The present study was conducted to assess the effect of glimepiride and repaglinide on atherosclerosis via interfering with the inflammatory and oxidative pathways.

Effects of glimepiride on study parameters

In this study we demonstrated that treatment with glimepiride appeared to have no significant effect on lipid parameters in comparison with the induced untreated group, and this may be due to the fact that change in lipid parameter induced by high fat diet overrides any changes expected from glimepiride. Moreover, in the present study glimepiride treatment significantly reduced the elevation of inflammatory markers (hs-CRP, IL-6 and TNF-α) in atherosclerosis model of hypercholesterolemic rabbit, suggesting that glimepiride inhibited vascular inflammation induced by high cholesterol diet. Glimepiride has been reported to show extra pancreatic actions including phosphorylation of insulin receptor substrate-1, which is

Table 2: Changes of body weight and rabbit's serum lipid profile [total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL)] in the four experimental groups. The data was expressed as Mean ± Standard Error of mean (SEM) (N = 6 in each group) using paired T-test

		Body weight (kg)	LDL (mg/dl)	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)
Normal control	Zero time	1.5 ± 0.2	63 ± 1.6	85 ± 2.92	43.3 ± 1.71	15.6 ± 1.28
	10 weeks	1.5 ± 0.9	68 ± 2.3	88 ± 3.26	45 ± 3.5	16.5 ± 1.4
Induced untreated	Zero time	1.6 ± 0.1	73 ± 1.9	90 ± 1.65	44 ± 2.87	16.2 ± 1.29
	10 weeks	1.4 ± 0.06	719 ± 14.62	994 ± 28*	324 ± 20.5*	37 ± 1.74*
Glimepiride 0.1 mg/kg	Zero time	1.54 ± 0.3	74 ± 3.57	91 ± 3.36	42 ± 2.17	16.4 ± 1.37
	10 weeks	1.67 ± 0.04	711 ± 22.75	977 ± 9.9	319 ± 9.2*	42.5 ± 3.08*
Repaglinide 0.3 mg/kg	Zero time	1.62 ± 0.03	66 ± 1.84	89 ± 4. 4	40 ± 2.89	15.7 ± 1.36
	10 weeks	1.68 ± 0.04	675 ± 14.58	957 ± 11.72*	320 ± 9.7*	40.6 ± 2.99*

**P<0.05, Where, TC = total cholesterol; TG = triglyceride; LDL = low density lipoprotein; HDL = high density lipoprotein (HDL).*

Table 3: Changes of rabbits serum inflammatory markers [high sensitive C - reactive protein (hs-CRP), Interleukin – 6 (IL-6) and Tumor Necrosis factor (TNF- α)] of the four experimental groups. The data was expressed as Mean ± Standard Error of mean (SEM) (N = 6 in each group) using paired T-test

		hs-CRP (mg/l)	IL-6 (pg/ml)	TNF-α (pg/ml)
Normal control	Zero time	3.5 ± 0.5	0.75 ± 0.1	0.6 ± 0.09
	10 weeks	4.3 ± 0.7	1.1 ± 0.09	1.05 ± 0.06
Induced untreated	Zero time	4.2 ± 0.9	1.06 ± 0.05	0.77 ± 0.1
	10 weeks	20.7 ± 1.7*	5.5 ± 0.5*	7.05 ± 0.44*
Glimepiride 0.1 mg/kg	Zero time	3.8 ± 0.3	1.1 ± 0.09	0.9 ± 0.1
	10 weeks	7.4 ± 1.1*	2.4 ± 0.2*	2.5 ± 0.2*
Repaglinide 0.3 mg/kg	Zero time	4.1 ± 0.5	0.9 ± 0.08	0.85 ± 0.05
	10 weeks	10.4 ± 0.6*	2.8 ± 0.3*	2.7 ± 0.17*

**P<0.05, Where, hs-CRP = high sensitive C - reactive protein; IL – 6 = Interleukin – 6; TNF- α = Tumor Necrosis factor.*

Table 4: The means' of rabbits' aortic Oxidative stress parameters [Malondialdehyde (MDA) and Glutathione (GTH) and reduced glutathione (GTH)] in the four experimental groups at the end of experiment have been given below. The data was expressed as Mean ± Standard error of mean (SEM) [N=6 in each group] using paired T-test

Group	Aortic MDA µmole/ gm aorta	Aortic GTH nmole/ mg aorta
Normal control	1.4 ± O.14	38.3± 2.46
Induced untreated	7.3 ± O.55*	21.7± 1.75*
Glimepiride 0.1 mg/kg	3.6 ± O.44	30.4 ± 2.2
Repaglinide 0.3 mg/kg	2.35 ± 0.26	34.5 ± 1.8

**P < 0.05, Where, MDA = Malondialdehyde; GTH = glutathione.*

a regulator of phosphaoltidylinosit 3-kinase (PI3-kinase) in adipocytes.[19] PI3-kinase has been shown to be involved in agonist-induced nitric oxide (NO) production in vascular endothelial cells.[20] Collectively, these findings suggest that glimepiride may stimulate NO production in endothelial cells through a PI3-kinase dependent pathway. Kenyon *et al.* have shown that the production of NO might be needed as a defensive factor in various models of acute or chronic inflammation.[21]

In addition to that, it was seen that glimepiride had significantly reduced aortic MDA levels suggesting a decrease in reactive oxygen species levels and subsequent lipid peroxidation. Also Glimepiride had significant effect on the aortic GSH levels, and prevented GSH depletion in hypercholesterolemic rabbit, and thus, helped to maintain an antioxidant balance which is important for vascular protection against lipid peroxide. There are two possible explanations for antioxidant capacity of glimepiride, firstly through inhibition of cellular cyclooxygenase pathways,[8] and the second possible mechanism may be related to the fact that glimepiride has the property to up-regulate antioxidant enzyme genes like paraoxonase, superoxide dismutase and catalase gene through reducing the activation of the redox sensitive nuclear factor kappa-B (NF-be),or through that glimepiride possessed agonistic activities for PPARγ.[22-24]

Also, glimepiride treatment significantly reduced aortic intima thickness in rabbits compared with the induced untreated group of rabbits. Atherosclerosis is now widely accepted as a chronic inflammatory process. Low-grade inflammation, enhanced oxidant stress and lipid peroxidation may predispose an individual to developing atherosclerosis. The athero-protective effect of glimepiride is due to interference with the inflammatory and oxidative pathways in hypercholesterolemic rabbits. In addition to that, glimepiride also specifically inhibits some processes in the early cellular events of atherosclerosis, which may

Table 5: The means of rabbit's aortic intima thickness of the four experimental groups at the end of experiment have been given below. The data was expressed as Mean ± Standard error of mean (SEM) (N = 6 in each group) using paired T-test

Group	Aortic intima thickness (µm)
Normal control	32.4 ± 2.7
Induced untreated	334.82 ± 53.5*
Glimepiride 0.1 mg/kg	203.03 ± 22.35*
Repaglinide 0.3 mg/kg	195.6 ± 23.1*

**P<0.05*

include: Adherence of circulating blood monocytes to vascular endothelial cells; migration of adherent monocytes into the sub endothelial space and their subsequent differentiation into macrophages; oxidative alteration of LDL mediated by vascular endothelial cells, smooth muscle cells, or macrophages; and, uptake of oxidative LDL by macrophages by scavenger receptors to generate foam cells.[25] Glimepiride has a inhibitory effect on cell-mediated LDL oxidation, and it may prevent the oxidation processes, and also reduce aortic intimal thickness while inhibiting the progression of atherosclerotic lesion.

Effects of repaglinide on study parameters

In the present study we found that repaglinide had no significant effects on lipid profile in comparison with the induced untreated group. This finding may be due to that the high cholesterol diet may mask any changes in the lipid parameter. Repaglinide is a new oral anti diabetic agent with a possible antioxidant activity. Therefore, in the present study we tested if repaglinide has a potential anti-inflammatory effect beyond its antioxidative activity, and if it has potential capability of controlling the initiation and progression of atherosclerotic lesions. The result of our study demonstrated a significant effect of repaglinide on inflammatory markers (hsCRP, IL-6 andTNF-α) in rabbits on a high fat diet, suggesting a possible anti-inflammatory activity of repaglinide on the vascular inflammatory responses induced by high fat diet. The possible explanation of anti-inflammatory effect of repaglinide could be related to it is antioxidative activity. Antioxidant agents might be practical therapeutic tools which interfere with the production of pro-inflammatory and cytotoxic mediators.[26] Esposito *et al.* showed that during glucose infusion, the rise in plasma cytokines induced by hyperglycemia was completely prevented by the antioxidant agent glutathione.[27]

Moreover, repaglinide significantly inhibited the increase of aortic MDA induced in high cholesterol-fed rabbits suggesting a decrease in reactive oxygen species and subsequent lipid peroxidation. Also, Repaglinide

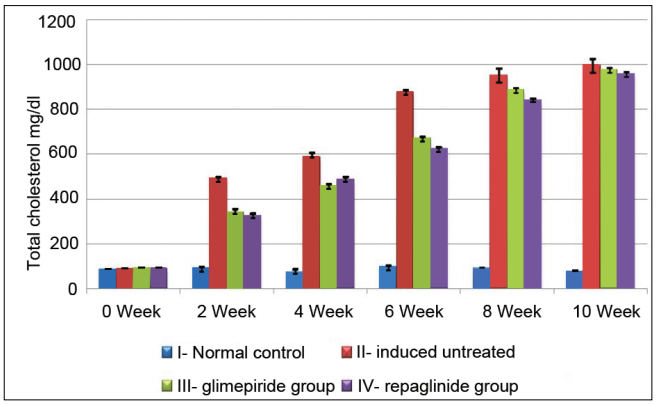

Figure 1: Effect of glimepiride 0.1 mg/kg /day and repaglinide 0.3 mg/kg /day treatment on serum total cholesterol (TC) levels (mg/dl) during the experimental treatment

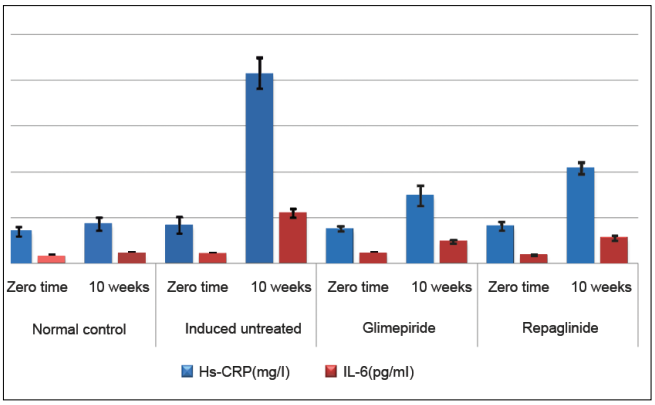

Figure 2: Effect of glimepiride 0.1 mg/kg /day and repaglinide 0.3 mg/kg /day treatment on serum high sensitive C - reactive protein (hs-CRP) (mg/l) and serum Interleukin – 6 (IL-6) (pg/ml) in comparisons to the two control group (normal and induced untreated)

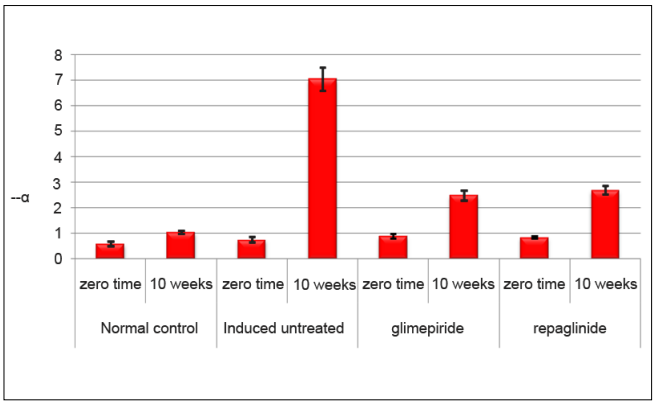

Figure 3: Effect of glimepiride 0.1 mg/kg /day and repaglinide 0.3 mg/kg /day treatment on serum tumor necrosis factor alpha (TNF-α) (pg/ml) in comparisons to the two control group (normal and induced untreated)

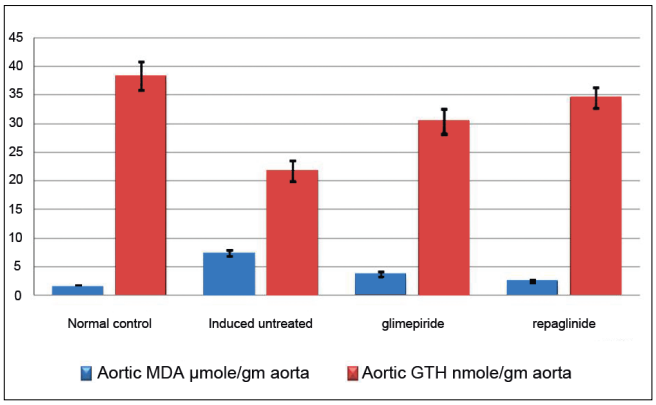

Figure 4: Effect of glimepiride 0.1 mg/kg /day and repaglinide 0.3 mg/kg /day treatment on aortic malondialdehyde (MDA) µmole/gm aorta and aortic glutathione (GTH) nmole/mg aorta in comparisons to the two control group (normal and induced untreated)

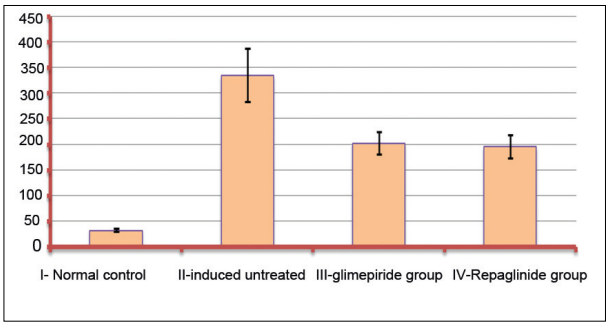

Figure 5: Effect of glimepiride 0.1 mg/kg /day and repaglinide 0.3 mg/kg /day treatment on aortic intimal thickness level (µm) at the end of experiment

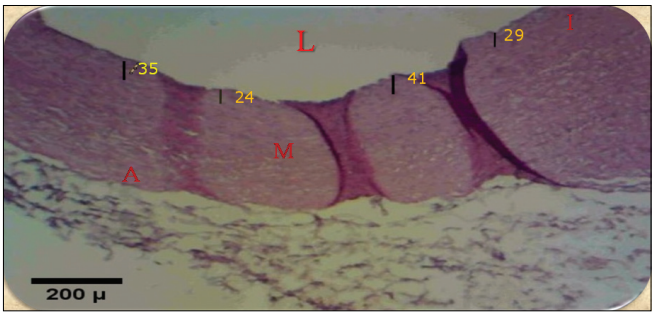

Figure 6: Photomicrograph of histomorphometric section in aortic arch of rabbits fed on normal diet for 10 weeks (normal control) show appearance of arterial wall layers: Lumen (L). Intact continuous endothelium, Intima (I), regularly arranged smooth muscle fibers, media (M) and adventitia (A). The section stained with hematoxylin and eosin (×10)

significantly increased aortic GTH level, and thus it prevented GSH depletion in hypercholesterolemic rabbits, and thus, maintained an antioxidant reserve which is crucial for vascular protection against lipid peroxide. Repaglinide is a benzoic acid derivative that lacks a sulfa group, hence the possible explanation of the antioxidant activity of repaglinide is due to its benzoic acid group.[28] Also, studies have demonstrated that benzoic acid derivatives could also have an antioxidant activity.[29]

The present study demonstrated that repaglinide treatment significantly suppresses the increase in intimal thickness

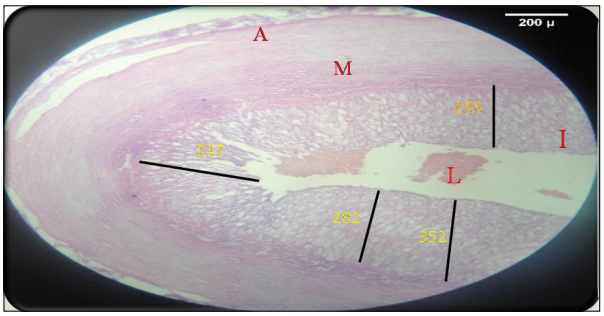

Figure 7: Photomicrograph of histomorphometric section in aortic arch of rabbits fed on normal diet for 10 weeks (induced untreated) show diffuse intimal thickening and confluence of lipid collections create an extracellular dense accumulation of fat in a wall determined area [Lumen (L), Intima (I), media (M) and adventitia (A)]. The section stained with hematoxylin and eosin (×10)

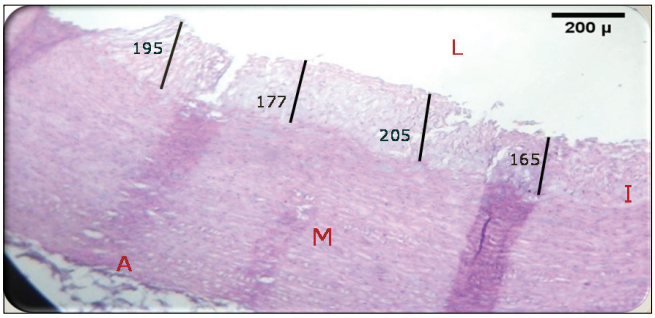

Figure 8: Photomicrograph of histomorphometric section in aortic arch of glimepiride hyperlipidemic rabbits, shows significant decrease in intimal thickness as compared to induced untreated [Lumen (L), Intima (I), media (M) and adventitia (A)]. The section stained with hematoxylin and eosin (×10)

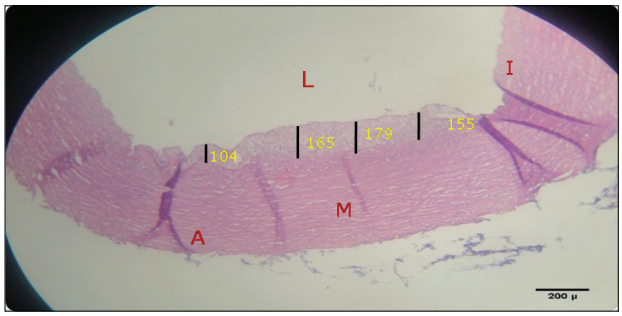

Figure 9: Photomicrograph of histomorphometric section in aortic arch of repaglinide hyperlipidemic rabbits, shows significant decrease in intimal thickness as compared to induced untreated [Lumen (L), Intima (I), media (M) and adventitia (A)]. The section stained with hematoxylin and eosin (×10)

induced by atherogenic diet in rabbits as compared with induced untreated group. In our study we found that Repaglinide treatment exerts an anti inflammatory effect by reducing levels of hsCRP, IL-6 andTNF-α and also an antioxidant effect by reducing lipid peroxide (MDA) levels and enhancing GTH. Thus, these findings may provide mechanistic answers as to how can repaglinide reduce aortic intima thickness via a number of pathways, including the suppression of systemic inflammatory response and oxidative stress.

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