A study of the effects Telmisartan on induced hyperlipidemia and atherosclerosis in male rabbits

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Abstract:

Atherosclerosis is a major killer disease world wide. The most common risk factors are diabetes, arterial hypertension, hyperlipidemia, obesity. The period of this study was continued for one year. This study explains the effect of Telmisartan on induced atherosclerosis in male rabbits. Eighteen local domestic rabbits were allocated randomly into 3 groups. Atherosclerosis was induced in 2 groups by adding cholesterol powder(3%) to standard chow diet for 10 weeks .Normal control group was put on normal chow diet. The blood sampling was collected firstly at the end of the induction period and every 5 days through the 60 days of treatment course, and serum lipid profile namely .TG,TC,LDL,VLDL,and HDL were measured .Autopsy of aortic (abdominal and thoracic) sectioning for histopathology were done before treatment and after completing the 60 days of treatment. Telmisartan show a significant reduction (P value<0.01) in serum cholesterol level, Triglyceride, LDL-cholesterol, VLDL-cholesterol ,and significant increase in HDL-cholesterol level as compared with control groups ($p<0.01$) ,Telmisartan treated group showed significant atherolytic effects ($p<0.001$) as compared with the untreated group.

We conclude that Telmisartan reduced serum levels of TC, TG, LDL, VLDL and increase serum HDL level in treated animals. Telmisartan decrees atherogenic index with atherolytic effect in arterial wall of treated animals.

دراسة تأثيرات التلميسارتان على تصلب الشرايين وزيادة الدهون المستحدث في ذكور الأرانب

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الخلاصة:

اجريت هذه الدراسة لمدة سنة على 18 ارنب محلي حيث وزعت إلىثلاثة مجاميع وتم احداث التصلب في مجموعتين منها بواسطة إعطاءها غذاء يحتوي على 3%كولسترول لمدة عشرة اسابيع ،اما المجموعة الثالثة (مجموعة السيطرة الطبيعية) اعطيت غذاء قياسي طبيعي وتم سحب عينات الدم عند نهاية فترة احداث التصلب وكل 5 ايام خلال 60 يوم من فترة المعالجة وذلك لقياس مستوى الدهون وهي الكولسترول الكلي، الكلسيريدات الثلاثية ،الكولسترول واطئ الكثافة ،الكولسترول واطئ الكثافة جدا ،والكولسترول عالي الكثافة كذلك تم فحص المقاطع النسيجية للأبهر ألبطني والرأسي، كان الهدف من هذه الدراسة بيان تاثير التلمسارتان على ارتفاع الدهون وتصلب الشرايين المحدث في ذكور الارانب ، التلمسارتان احدث تناقص معنوي عالي في مستوىكلا من الكولسترول الكلي، الكلسيريدات الثلاثية

،الكولسترول واطئ الكثافة ،الكولسترول واطئ الكثافة جدا،وارتفاع معنوي في مستوى الكولسترول عالي الكثافة في مصل الدم اما الفحص النسيجي للابهر البطني والراسي التلمسارتان قلل معنويا التصلب الشرياني مقارنة مع المجموعة الغير معالجة.

Introduction:

Atherosclerosis is the leading cause of death in the developed world, and it is predicated to be the leading cause of death in the developing world within the first quarter of this century . [1,2].

Atherosclerosis is responsible for more than half of the yearly mortality in the United States and more than 500.000 people die annually of myocardial infarction in persons older than 50 years ,also it was more common among men than among women .[3,4].

Cerebrovascular disease is responsible for over 200,000 deaths per year in the united states [4]. The most common risk factors are ,Diabetes ,arterial hypertension ,hyperlipidemia ,obesity.[5].

The significance of atherosclerosis in diabetes is underscored by finding that 80% of death in the diabetic population are related to atherosclerotic disease such as stroke ,myocardial infarction ,and peripheral vascular disease.[6,7,8,9].

Hypertension is associated with morphologic alterations of the arterial intima and functional alteration of the endothelium that has similar to the changes observed in hypercholesterolemia and established atherosclerosis[10].Hyper-tension has been shown in both epidemiologic and experimental studies to accelerate atherosclerotic vascular disease and increase the incidence of clinical complication.[11]

Materials and Methods:

The study was conducted on 18 local domestic rabbits . They were divided into 3 groups (6 in each group).The period of this study was continued for one year in Kufa Medical College animals house and exposed to controlled temperature around 25c and artificial 12 light-dark cycles were left for 2 weeks without interference for acclimatization .All rabbits were males aging from 4-6 with the 12.00 a.m being the mid-dark period .Rabbits were allowed to drink water *ad libitum* .They months .Their body weight had ranged from 1000-1100 grams .They had no manifestation of any illness upon examination .Standard chow diet and water were given ad labium during day after witch time those rabbits were fasted overnight starting at 01:00 a.m to obtain the fasting blood samples at 11:00 in the morning . All rabbits groups except group A were induced with atherosclerosis by giving daily (3% cholesterol) made by adding cholesterol powder to standard chow diet for 10 weeks[12] .

After 10 weeks of cholesterol rich diet, blood samples from these 18 rabbits were taken and analyzed for lipid profile which showed hyperlipidemia and these 18 rabbits were enrolled in this study.

Animals in normal control group were also studied biochemically and histopathologically.

The results were expressed as mean ± S.D. students *t* test. And regression coefficient analyses were used for the assessment of the results of treated groups and control groups .The [ANOVA] analysis was used for the comparison of difference among the groups .

Chi-square test was used to compare between the proportion of histopathological changes in various groups . p. value <0.05 was considered to be statistically significant.

Results:

Effect on total cholesterol

Telmisartan (5 mg /kg/day) for 60 days treatment caused significant reduction in mean serum cholesterol level ($p<0.01$) .While no significant changes in rabbits serum cholesterol level in normal and untreated control groups (Table 1).

Table (1): The mean serum cholesterol concentrations (mg/ dl) in response to treatment with different agents for 60 days

Days of examination	The means of rabbits serum cholesterol concentrations in mg / dl		
	Normal	Induced untreated	Telmisartan (5mg/kg.BW)
Zero time	93± 2.39	510.75± 5.45	506.25± 4.64
5th	93.50± 2.66	500.50 ± 4.03	487.50± 3.55
10th	91.75± 2.55	500.12± 2.87	468.00± 4.57
15th	90.4± 1.08	502.00± 3.30	440.50± 1.29
20th	92.75± 1.30	503.50± 8.88	406.00± 10.72
25th	89± 1.89	494.00± 3.40	380.00± 4.86
30th	94.20± 1.42	497.50± 1.83	359.50± 2.99
35th	90.80± 0.61	491.50± 1.71	305.00± 6.27
40th	94.50± 2.05	488.50± 1.25	255.00± 5.23
45th	92.35± 0.95	490.50 ±1.26	195.00± 5.07
50th	90.20± 1.29	490.50± 1.50	165.50± 3.87
55th	91.30± 1.15	489.15± 2.30	126.00± 5.75
60th	93.05± 0.67	487.35±4.55	112.50± 4.36

Values are expressed as mean ±SD

Effect on Triglyceride

Rabbit serum triglyceride concentrations were markedly reduced by treatment with Telmisartan (5mg/kg /day) for 60 days ($p<0.01$). Triglyceride remained with no significant change in normal control group with significant increase in the induced untreated group as compared with normal group($p<0.01$) (Table2).

Table(2):Mean serum triglyceride concentrations (mg/ dl) in response to treatment with different agents for 60 days.

Days of examination	The means of rabbits serum triglyceride concentrations in mg / dl		
	Normal	Induced untreated	Telmisartan(5mg/kg.BW)
Zero time	102.75± 4.50	190.25± 1.89	187.75± 2.06
5th	97.25± 2.06	193.75 ± 4.50	181.00± 1.41
10th	95.00± 5.09	190.25± 1.26	170.00± 1.41
15th	100.50± 4.43	191.75± 3.30	159.50± 1.00
20th	100.00± 8.12	189.75± 0.96	151.00± 0.82
25th	95.00± 5.09	188.5± 1.29	145.25± 1.89
30th	96.00± 4.24	188.75± 6.70	142.00± 2.16
35th	97.35± 6.02	192.25± 2.22	132.00± 2.45
40th	102.25± 2.22	190.00±1.41	125.83± 0.57
45th	96.25± 5.38	188.00± 1.83	118.75± 0.96
50th	97.75± 6.65	188.00± 2.71	98.78± 0.450
55th	99.25± 4.34	186.00± 0.82	91.00± 1.41
60th	95.00± 5.09	183.75± 2.50	83.75± 0.96

Values are expressed as mean ±SD

Effect on HDL-Cholesterol

Serum HDL-cholesterol levels revealed that Telmisartan (5mg/kg/day) for 60 days of treatment caused significant increase in HDL-cholesterol level ($p<0.01$) as compared with control group.But there were significant decrease in serum HDL-cholesterol concentration in the untreated group ($p<0.01$) as compared with normal control group (Table 3).

Table (3): Mean serum HDL concentrations (mg/ dl) in response to treatment with different agents for 60 days.

Days of examination	The means of rabbits serum HDL concentrations in mg / dl		
	Normal	Induced untreated	Telmisartan (5mg/kg.BW)
Zero time	17.35± 0.93	13.375 ± 0.57	13.55± 0.69
5th	17.80± 0.40	14.10± 0.84	14.15± 0.51
10th	17.78± 0.94	13.83± 0.35	15.38± 0.75
15th	17.25± 0.96	13.65± 1.12	15.30± 0.95
20th	15.85± 0.69	13.85± 0.66	16.03± 0.58
25th	17.58± 0.72	14.20± 0.40	17.03± 0.21
30th	18.43± 0.43	13.60 ± 0.28	16.85± 0.71
35th	17.18± 0.62	13.20± 0.85	16.85± 0.44
40th	17.48± 0.43	13.87± 0.25	18.23± 0.56
45th	16.93±0.15	13.95± 0.76	20.38± 1.49
50th	18.63± 0.48	13.70± 1.27	20.50± 1.00
55th	17.70± 0.94	12.75± 0.45	21.25± 0.92
60th	17.53± 0.46	12.45± 0.42	22.60± 0.59

Values are expressed as mean ±SD

Effect on LDL-cholesterol .

Serum LDL-cholesterol level was increased in the induced untreated group as compared with that of the normal controlled group ($p<0.01$)(table 10,11).Although normal control group shows insignificant difference in LDL-cholesterol level. Telmisartan 5mg /kg /day for 60 days treatment caused significant reduction in rabbit serum LDL-cholesterol level ($p<0.01$) as compared with that of the control groups (Table 4).

Table (4): Mean serum LDL concentrations (mg/ dl) in response to treatment with different agents for 60 days.

Days of examination	The means of rabbits serum LDL concentrations in mg / dl		
	Normal	Induced untreated	Telmisartan (5mg/kg.BW)
Zero time	54.28± 2.70	456.28± 4.76	454.13± 5.19
5th	54.60± 3.27	450.35± 3.30	437.88± 3.81
10th	56.75± 1.41	470.43± 47.57	417.38± 5.29
15th	45.83± 2.06	448.98± 5.88	392.98± 1.68
20th	57.48± 2.31	449.50± 8.75	358.93± 24.29
25th	52.80± 2.63	444.80± 3.71	330.18± 4.53
30th	55.65± 1.56	445.90± 2.60	314.73± 2.58
35th	54.03± 1.53	439.33± 1.89	264.75± 6.39
40th	56.25± 2.57	437.48± 1.71	210.70± 4.56
45th	56.50± 1.24	438.13± 1.19	152.58± 6.06
50th	53.60± 2.67	439.43± 1.77	122.25± 5.82
55th	54.30± 1.97	441.25± 1.26	85.10± 6.51
60th	56.88± 0.89	434.25± 4.43	73.93± 4.61

Values are expressed as mean ±SD

Effect on VLDL-cholesterol

Serum VLDL-cholesterol level shows significant Reduction during the period of treatment (60 days) with, Telmisartan 5mg/kg/day ($p<0.01$) as compared With control groups (Table5). Serum VLDL-cholesterol level showed significant increase in the untreated control group along 60 days of treatment with D.W as compared with normal control group ($p<0.01$) (Table 5).

Table (5): Mean serum VLDL concentrations (mg/ dl) in response to treatment with different agents for 60 days.

Days of examination	The means of rabbits serum VLDL concentrations in mg / dl		
	Normal	Induced untreated	Telmisartan(5mg/kg.BW)
Zero time	20.55± 0.90	37.37± 0.66	37.50± 0.38
5th	19.48± 0.41	38.78± 0.88	36.20± 0.28
10th	19.00± 1.01	38.00± 0.33	33.95± 0.34
15th	20.10± 0.89	38.40± 0.57	31.90± 0.20
20th	19.98± 1.52	37.93± 0.22	30.35± 0.24
25th	19.00± 1.02	37.35± 0.47	29.05± 0.38
30th	19.10± 0.84	37.35± 0.94	28.38± 0.48
35th	19.40± 1.29	37.50± 0.58	26.40± 0.49
40th	20.10± 0.66	37.85± 0.68	15.10± 0.20
45th	18.85± 1.30	37.60± 0.28	23.75± 0.19
50th	19.05± 1.90	37.25± 0.50	19.55± 0.38
55th	19.85± 0.87	36.70± 0.48	18.20± 0.28
60th	19.00± 1.02	36.50± 0.58	16.75± 0.19

Values are expressed as mean ±SD

Histopathological finding

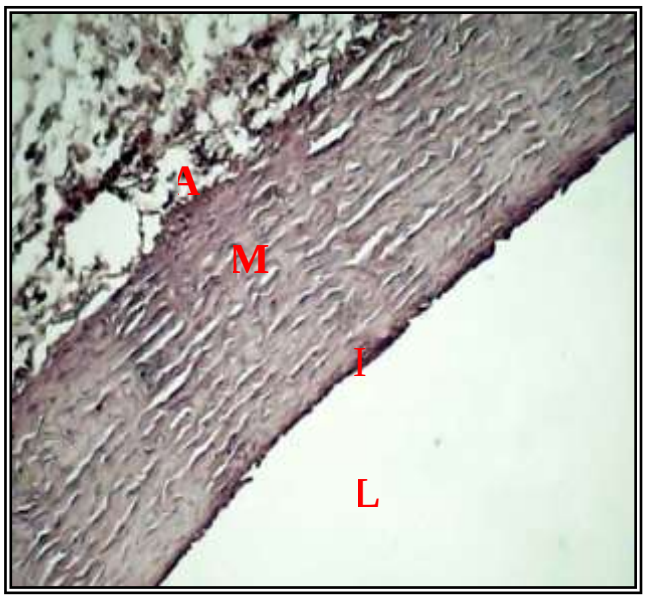
Atherosclerotic lesions were assessed in the rabbit's aortic arteries at the end of 60 days treatment.

The lesions were classified microscopically according to the (Daley SJ *et al.*, 1994) [13] for classification of atherosclerosis and to assess the degree of their severity. Telmisartan and Rosiglitazone treated groups showed significant atherolytic effects compared with untreated induced rabbits, Telmisartan 5mg/kg/day has the most potent effect as it had 50%of rabbits were with normal appearance of aortic artery cross section ,33%with phase 1(Fatty streak)and 17% with phase 2(diffuse intimal thickening**)**,0% with phase 3,4 **(**fibrous atherosclerotic plaque), (complicated lesion) as compared with the untreated($p<0.001$) (Table 6) Atherosclerosis induced group had virtually a 100% involvement of aortic artery with different phases of atherosclerosis .but Across section of normal rabbit thoracic aorta of normal control group shows the normal appearance of arterial wall layers after 60 days treatment by D.W .

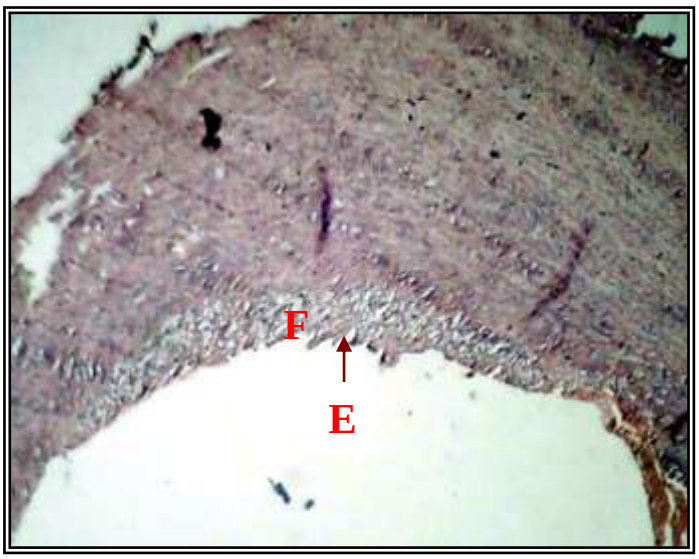
Table (6) Demonstrates aortic artery atherosclerotic lesions for group of rabbit autopsies After 60 days treatment course expressed as percentages and numbers of rabbits having different histopathological phases of severity.

groups	Percentages and numbers of histopathological phases of Rabbit's aortic artery involvement in atherosclerosis after 60 days of treatment as compared with the controls.						Significance
		Normal	Phase1	Phase2	Phase3	Phase4	
Normal control group NO.6	NO	6	0	0	0	0	N.S
	%	100	0	0	0	0	
Untreated control group NO.6	NO	0	1	3	1	1	N.S
	%	0	17	50	17	17	
Telmisartan, 5mg/kg/day. NO.6	NO	3	2	1	0	0	* P<0.001
	%	50	33	17	0	0	

Groups, at P-value <0.05.



Figure(1):Histological section of normal rabbit thoracic aorta shows the normal appearance of arterial wall layers, (I)Intact continuous endothelium (Intima) ,(L) lumen ,(M) regularly arranged smooth muscle fibers of elastic layer of aorta (media) ,(A)adventitia. Stained with haematoxylin and Eosin (x40).



Figure(2):A cross section in aortic artery of an experimental hypercholesterolemic rabbit ,demonstrating intima with many lipid laden macrophage (foam cells),that represent an early atherogenetic event (fatty streak) , (E) disrupted aortic endothelium ,(F)foam cells collection with intra cellular lipid droplets, (phase 1). The section stained with haematoxylin and eosin stain (x40).

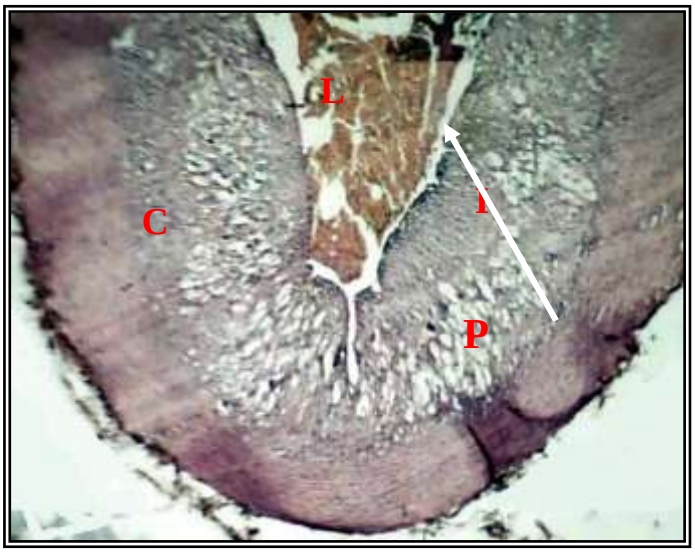
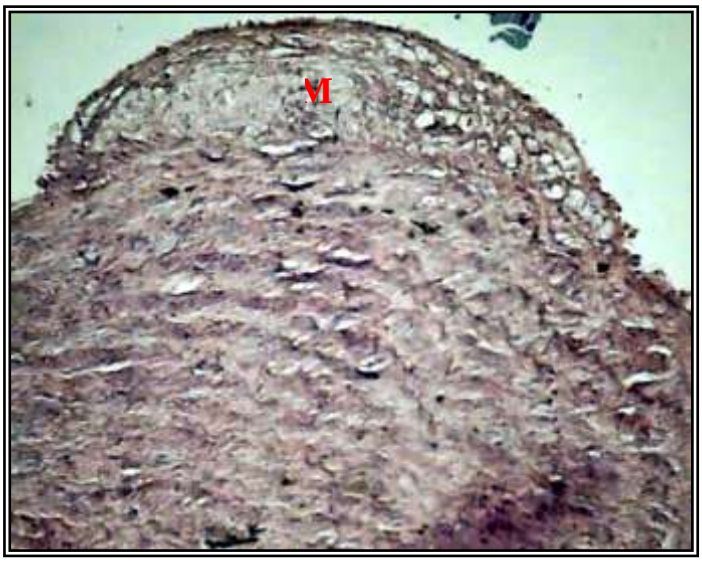


Figure (3):Section from aorta shows diffuse intimal thickening(I),and marked lipid and collagen collection within intima ,(P)intracellular and extracellular lipid collection (C) collagen ,(L) narrowing of lumen .phase 2 of atherosclerosis with haematoxylin and eosin stain (x40).



Figure(4):Histological section through the fibrous atherosclerotic plaques in rabbit aorta shows an atheromatous plaque toward arterial lumen (M) macrophages underline a thin layer of SMCS which is a phase 3 of atherosclerosis with haematoxylin and eosin stain (X40).

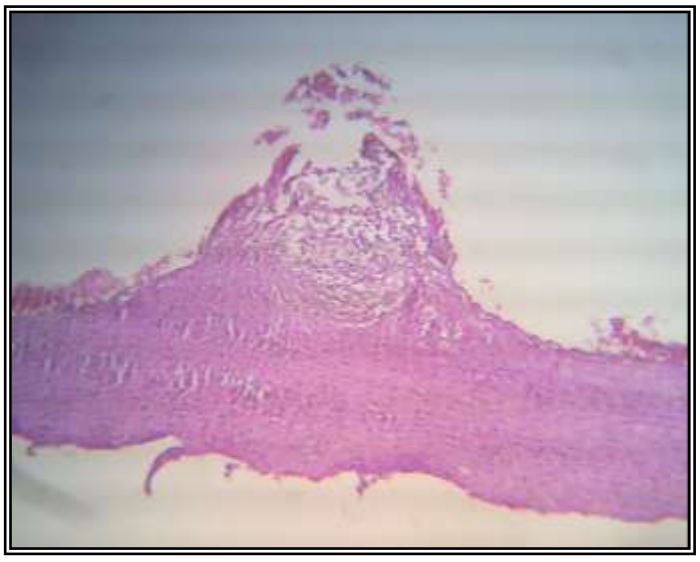


Figure (5):An aortic cross section shows surface defect of atheromatous plaque,(P)Luminal intrusion of atheromatous plaque ,(E)rupture of aortic endothelium ,phase 4 of Atherogenesis section stained with haematoxylin and eosin stain (X10).

Discussion:

Effect of Telmisartan

In the present study it was found that Telmisartan 5mg/kg/day caused significant reduction in serum total cholesterol level ($p<0.01$),with negative regression coefficient ($r=-0.99$) as compared with untreated group ($p<0.01$).These findings are similar to the finding of Derosa *et al.*,2004 ([14]),Sugano *et al.*, 1996 [(15)].This finding is due to inhibiting angiotensin 11and activating PPARg by Telmisartan [(16,17)].In addition, there is significant reduction of

rabbit serum TG level and VLDL level ($p<0.01$),with negative regression coefficient (-0.99,-0.99),The same results was found by Benson *et al.*, 2004 [17],Derosa *et al.*, 2004 [14],and Derosa *et al.*, 2004 [18] ,who attributed it to insulin sensitization, PPARg activation,and decreases fatty acids , [17, 16]

Also we found that Telmisartan 5mg/kg/day causes highly significant increase in serum HDL-cholesterol level ($p<0.01$),our results are in agreement with that obtained by Derosa *et al.*, 2004 [14],Derosa *et al.*, 2004 ([18] and Schupp *et al.*, 2004 [17].This effect can be explained by the fact that Telmisartan acts as a partial agonist of PPAR- g [16].

Rabbits LDL - cholesterol concentration were significantly reduced by Telmisartan ($p<0.01$) .This finding is contrary to that reported by ,Keidar *et al.*, 1997 [19],Schupp *et al.*, 2004 [17] , Schuh ,1993 [20].This could be attributed to the inhibition of Angiotensin 11and activation of PPARg by Telmisartan [19].

Histopathological examination of autopsy specimens of rabbits at the end of the 60 days treatment with Telmisartan showed Improvement in the severity of atherosclerosis lesion as the phase of atherosclerosis decreases ,Telmisartan treated group had most potent atherolytic effect as it had 50% of rabbit with normal appearance of aortic cross section,33%with phase 1,and 17% with phase 2,0% with phase 3 and phase 4.as compared with the untreated($p<o.oo1$).

These atherolytic effects in our result are similar to the finding of Heres,1999 [21], Wong, 2004 [22], Mcmurrau, 2004 [23], Nissen, 2004 [24], Teo, 2004 [26], Disertori,2005 [25], Schuh, 1993 [20].

This can be explained by the fact that Telmisartan inhibits of LDL lipid peroxidation uptake into endothelial cells ,and it is known that oxidized LDL accelerate early proatherosclerotic processes before macrophage participation in the

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