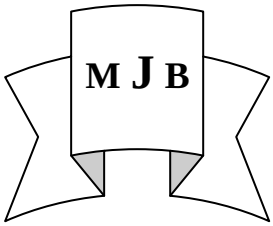
Study Effect of Glimepiride and Repaglinide on CIMT and Long Glycemic Control in Type 2 Diabetic Patients Double Blind Study

Hussein Aziz Naser
Dept. of Medicine , College of Medicine, University of Kufa,



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Abstract

Background Diabetes mellitus (DM) is one of the main risk factors for cardiovascular complications ,namely coronary ischemia, Peripheral vascular disease, and stroke. Atherosclerosis is highly associated with Diabetes mellitus . Carotid intima media thickness (CIMT) is used extensively as a method to detect atherosclerosis.

Aim of the study repaglinide and glimepiride are newly introduced and used for non–insulin-dependent diabetes mellitus (NIDDM) ,the study aim to compare the difference in their effect on CIMT.

Patients and Methods The study enrolled 62 patients NIDDM all from Al Hakeem Diabetic center in Najaf in period from January 2011 to the March 2012 all had their recording files with mean age (53±0.23), 35females and 27 males with body mass index (BMI) Mean(28±0.4) divided into two groups (blindly grouped) each one 31used Repaglinide 3mg/day and second one used Glimepiride 3mg/day. followed after 6 months and then after 12 months record the hemoglobin A_{1c}(HbA_{1c}), lipid profile , CRP, blood pressure ,the blood urea and serum Creatinine and studying the CIMT of both internal carotid and the common carotid arteries using ultrasonic Doppler study .

Results There was a significant($p<0.05$) reduction in CIMT of left internal carotid and the right common carotid arteries in patients treated with repaglidine compares to those patients treated with glimepiride and there was also reduction in the other parameters Low-density lipoprotein (LDL) , Triglyceride (TG) ,HbA_{1c} still these decrement were not a significant one.

Conclusion and recommendation repaglinide is better in reduction of the CIMT than Glimepiride in spite of insignificant reduction in the lipid profile or HbA_{1c}. We recommend to study what dose required to achieve a best reduction in CIMT.

Key Words : diabetes ,glimepiride, repaglinide, CIMT.

الخلاصة

دراسة مزدوجة غير محددة لتاثيرعقار كلمبرايد وعقار رابكليدين على ثخن الطبقة المبطنة الداخلية للشرايين العنقية في النوع الثاني لمرض السكري مرض السكر يشكل احد اخطر عوامل مضاعفات إمراض جهاز الدوران و الأوعية الدموية وبالأخص عدم كفاءة الشرايين القلبية وإمراض الأوعية الدموية للأطراف والجلطة الدماغية إن تصلب الشرايين يتصاحب مع مرض داء السكر وان قياس ثخن الطبقة المبطنة الداخلية للشرايين العنقية يستخدم بشكل واسع للتعرف على تصلب الشرايين–تهدف الدراسة إلى مقارنة الفرق في التأثير بين العقارين على ثخن الطبقة المبطنة الداخلية للشرايين العنقية–شملت الدراسة٦٢مريضا من النوع غير المعتمد على الأنسولين في مركز الحكيم للسكري في الفترة بين كانون الثاني٢٠١١واذار٢٠١٢وكان عمر المصابين بالمتوسط ٥٣،٢ سنة وتوزعوا على ٣٥ من الإناث و٢٧ من الذكور وبمعدل كتلة الجسم ٢٨،٤وقد وزع المرضى وبشكل غير محدد على مجموعتين ٣١استخدموا كلمبرايد ٣ملغم و٣١استخدموا ٣ملغم رابكلدين تم إعادة فحص ثخن الطبقة المبطنة الداخلية للشرايين العنقية بواسطة جهاز الأمواج فوق الصوتية بعد ٦شهور وبعد ١٢شهرا مع دراسة مستوى الدهون وحساب معدل السكر التراكمي أثبتت النتائج الإحصائية أن عقار رابكليدين أفضل من عقار كلمبرايد في خفض تخن الطبقة المبطنة الداخلية للشرايين العنقية.

Introduction

Multiple risk factors interventional trial (MRFIT) suggested that the prevalence of atherosclerosis is two to three times in diabetic patients than in those without diabetes[1]. Atherosclerosis is the cause of morbidity in 70% of patients with type 2 DM [2]. Hyperglycemia induces endothelial dysfunction along with hypercoagulability potential of DM causes acceleration in the process of atherosclerosis complications. DM enhances the plague vulnerability, increases the inflammation and neovascularization. Post mortem studies provided multiple observational evidences related to the increased abundance of macrophages, neovessels in diabetic atheroma. Increased inflammation induces the increased in heme oxygenase -1(HO-1) in DM. In order to attenuate the oxidative stress HO-1 induction is modulated by the peroxisome proliferation activator receptors (PPAR)[4]. PPAR alpha and PPAR gamma and ligands and advanced glycation end products (AGE) associated with DM (Evans et al, 2004)[3].DM with increased proinflammation and proatherogenic and additional oxidative stress with AGE proteins facilitates increased need for HO-1 in DM plagues. Studies from Hisayama cohort study clinical trial and autopsy derived plagues from DM associated human atherosclerosis indicates a significant HO-1 proteins expression when compare to non DM (Song et al.2009).This is due to impending need of HO-1 to balance and counter regulate the oxidant stress and the inflammatory process which is apparently mediated by the HO-1 enzymes system against the oxidative and inflammatory activation .The vessel wall responds to antagonize the deleterious effects of heme at three different levels Extracellular, Cellular membrane and Intracellular level. In ordinary condition endothelium is resistant to the leukocytes adhesion but hypercholestremia promotes leukocyte adhesion to endothelium. Oxidized LDL reduces intracellular concentration of nitrous oxide (NO) and cause endothelial activation[2]. Angiotensin II has an important role in endothelial dysfunction it opposes NO action and increases production of reactive oxygen species (ROS) which increases expression of proinflammation cytokines like 1LK, monocyte-chemotract protein-1(MCP-1) and also unregulated vascular adhesion molecule-1 (VCAM-1). These endothelial coupled with elevated acute phase protein (CRP) level set the stage of initiating and progression of atherosclerosis promoting inflammation within the vessel wall[2]. There are four theories to explain the association of hyperglycemia with atherosclerosis .First is the increased polyol pathway. Second increased advanced glycation end products (AGE).Third is the activation of protein kinase C (PKC) isoforms and fourth increased hexosamine pathway flux. Measurement of the carotid intima media thickness CIMT is a noninvasive test where the lining of the carotid arteries is measured with the use of B-mode ultrasound. The intima is the innermost layer of the artery, and the media is the middle layer of the artery. CIMT persisted as an independent in the three cohorts after full or partial adjustment for Framingham risk factors[6].The meta analysis demonstrated that studies showing positive association between CIMT and plasma level of C-reactive protein(CRP)or fibrinogen are in majority[13].Lorenz et al 2007 conducted a systematic review of the literatures to provide clinical cardiovascular end points. The review found that CIMT is a strong predictor of future vascular events but it did not

consistently improve the risk classification of individual. American Diabetes Association and American College of cardiology foundation report included the following statement regarding CIMT measurement.(The presence of so called subclinical vascular disease may be determined by measuring calcification, CIMT or the ankle-brachial index. Patients with documented subclinical atherosclerosis are at increased cardiovascular disease risk and may considered candidates for more aggressive therapy)7 The recommendation of American Society of Echo cardiology according to (Stein, et al,2008) concluded that measuring CIMT and identifying carotid plague by ultrasound are most useful for refining cardiovascular risk assessment in patients at intermediate cardiovascular risk(Framingham risk) score6-20%without established coronary heart disease, peripheral arterial disease, cerebral vascular disease, diabetes mellitus or aortic aneurysm[20]. repaglinide is antidiabetic oral agent of the new glidine class with insulin tropic activity [10], Its action on insulin secretion is more rapid and shorter than that of sulphonylurea compounds. Glimepiride is an oral blood glucose lowering drug of the sulphonylurea class. It is classified as third generation, act as secretagogogue and it increases activity of intracellular insulin receptors[8].

Patients and Methods

62 patents NIDDM all had their recording files in Al Hakeem diabetic center in Sadar teaching hospital in Najaf enrolled in the study from January 2011 to March 2012 and the patients were randomized either to receive either a fix dose of repaglinide 3mg/day or 3mg/day glimepiride for one year and review was done after 6 months from start of the study ,and then after 12 months. The parameters used in the study included CIMT of both internal carotid and common carotid ,HbA_{1c}, LDL, TG, HDL(high-density lipoprotein), Serum cholesterol, CRP, Blood urea and Serum Creatinine, Blood pressure and protienurea. Inclusion criteria were previously known type 2 diabetic patients treated with oral hypoglycemic agents , age 35-75 years, HbA_{1c}>6.6.Exclusion criteria include significant elevation in the hepatic enzyme alanine aminotransferases elevation >2.5 folds in gender specific normal value or renal disease (serum Creatinine >1.2).absence of congestive heart failure (NYHA class2 to 4), cigarette smoking, absence of aortic stenosis or carotid arterial obstruction .CIMT was evaluated with high resolution ultrasonic Doppler type (Toshiba Xavio) (Figure 1).

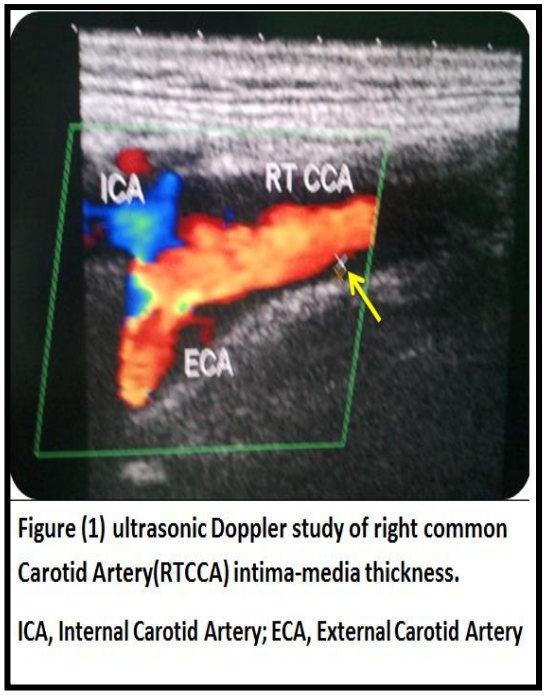

Figure (1) ultrasonic Doppler study of right common Carotid Artery(RTCCA) intima-media thickness.

ICA, Internal Carotid Artery; ECA, External Carotid Artery

Every patient was evaluated 3 times by a single operator at intervals of 6 months and 12 months. On a longitudinal two dimensional ultrasound image of the carotid artery, the anterior (near) and posterior (far) wall of the carotid artery are displaced as two bright white lines separated by hypoechogenic space. The distance between the leading edge of the first

bright line of the far wall (luminal-intimal interface) and the leading edge of the second bright line (media-adventia interface) indicates the intima-media thickness, the procedure was repeated on both sides. The interfaces of the distal common carotid artery were marked across a length of 10 mm. The beginning of dilatation of distal common carotid artery served as reference point for start of the measurement. At least 3 readings were taken and the average of 3 readings of CIMT was taken for evaluation the CIMT of both right and left sides was calculated and average of 2 values was also taken.

Photometric HbA_{1c} assay was done by mixing 100µLwhole blood with500uL glycine for 10 minutes then 20uL from the mixture is taken and added to it 5 mmol water and tested with 410 nanometer photometry.

The lipid profile was studied by ARCHITECT plus Abbott type instrument. All statistical analysis was obtained using statistically package for social sciences(SPSS) version 20 computer software. All data of each set expressed as mean±SD.

Patient data according to age groups

Group 1the age of patient (35-44)year

sex	BMI	HbA_{1c}	CRP	BP	UREA	CR	CHOL	TG	HDL	LDL	PU	Lt Ic MIT	RT IC MIT	M IC MIT	LT CC MIT	RT CC MIT	M CC MIT	D
F	28.4	8.2	4.6	130/80	32	0.8	225	130	40	110	-ve	0.07	0.07	0.07	0.07	0.07	0.07	2
F	31.2	8.3	8.6	130/80	34	0.8	180	170	45	85	-ve	0.07	0.07	0.07	0.07	0.08	0.075	1
F	23.6	6.8	3.1	130/80	29	0.9	225	175	47	105	-ve	0.06	0.05	0.055	0.05	0.05	0.05	1
F	31.5	9.2	4.1	120/80	32	0.8	187	150	44	95	-ve	0.05	0.05	0.05	0.05	0.05	0.05	2
F	26.6	8.4	5.1	130/80	34	0.7	193	175	47	105	-ve	0.06	0.06	0.06	0.06	0.06	0.06	1
F	26.2	7.5	2.3	120/80	31	0.8	175	121	34	80	-ve	0.09	0.09	0.09	0.08	0.08	0.08	1
M	27.1	9.0	5.5	120/80	36	0.8	230	180	36	115	-ve	0.07	0.07	0.07	0.07	0.07	0.07	2
F	25.9	7.8	3.6	140/83	30	0.8	210	348	38	120	-ve	0.06	0.07	0.65	0.07	0.07	0.07	1
M	34.37	8.1	4.4	120/70	28	0.6	205	218	30	110	-ve	0.06	0.06	0.06	0.06	0.06	0.06	2
F	30.7	19.2	3.3	120/80	35	0.8	270	230	35	105	-ve	0.06	0.06	0.06	0.06	0.06	0.06	1
M	24.82	10.8	4.5	120/70	28	0.8	260	160	42	110	-ve	0.08	0.07	0.075	0.08	0.08	0.08	2
M	42.1	8.9	402	150/90	30	1	240	140	40	95	-ve	0.06	0.06	0.06	0.06	0.065	0.062	2
M	24.3	12.8	2.4	110/80	30	6.6	210	160	35	95	-ve	0.08	0.09	0.08	0.08	0.09	0.09	1
F	24.2	14	4.6	120/80	26	0.5	180	135	42	85	-ve	0.06	0.07	0.065	0.07	0.07	0.07	1
M	23.6	9.2	3.2	110/70	28	0.6	170	110	35	110	-ve	0.03	0.03	0.03	0.03	0.03	0.03	1
F	24.2	8.8	4.1	110/70	26	0.7	190	170	45	96	-ve	0.07	0.06	0.65	0.08	0.06	0.07	2
M	26.5	12.5	12.3	140/90	28	0.8	220	205	32	125	-ve	0.09	0.09	0.09	0.08	0.08	0.08	1
F	25.1	10.2	4.6	120/85	26	0.4	280	170	38	110	-ve	0.07	0.06	0.65	0.08	0.08	0.08	2
F	21.1	8.1	4.8	110/70	28	0.6	180	175	35	85	-ve	0.06	0.06	0.06	0.15	0.06	0.055	1
M	29.07	13.4	17.2	130/85	28	0.9	220	135	35	105	-ve	0.07	0.07	0.07	0.08	0.08	0.08	2
F	23.7	8.2	2.3	110/70	28	0.6	182	115	40	95	-ve	0.06	0.06	0.06	0.06	0.06	0.06	2
M	26	12.8	8	120/75	27	0.8	235	168	32	112	-ve	0.07	0.07	0.06	0.06	0.06	0.06	1
M	28.6	10.5	15.2	120/80	26	0.6	265	135	35	115	-ve	0.06	0.06	0.06	0.06	0.06	0.06	1

Group 2 the age of patient (45-54) year

sex	BMI	HbA_{1c}	CRP	BP	UREA	CR	CHOL	TG	HDL	LDL	PU	Lt Ic MIT	RT IC MIT	M IC MIT	LT CC MIT	RT CC MIT	M CC MIT	D
M	25.6	8.4	6.6	120/80	30	0.6	220	170	35	110	-ve	0.08	0.07	0.075	0.08	0.08	0.08	1
M	30.9	7.1	2.1	120/80	35	0.9	228	118	35	105	-ve	0.06	0.07	0.065	0.07	0.08	0.075	1
M	26.4	8.9	4.6	130/80	32	0.8	106	170	34	110	-ve	0.06	0.06	0.06	0.06	0.06	0.06	2
F	31.96	12.1	4.3	140/80	32	0.6	222	164	44	95	-ve	0.09	0.09	0.09	0.08	0.08	0.08	2
F	25.78	11.2	136	130/80	18	0.83	193	138	40	110	-ve	0.09	0.08	0.085	0.08	0.08	0.08	2
M	2.5	8.2	3.2	120/80	32	0.8	220	165	40	105	-ve	0.08	0.09	0.08	0.08	0.07	0.075	1
M	27.3	10.2	4.6	120/70	26	0.8	240	210	34	130	-ve	0.08	0.08	0.09	0.08	0.08	0.08	1
F	26.1	8.4	6.1	120/85	28	0.8	205	180	43	92	-ve	0.08	0.07	0.75	0.09	0.09	0.09	1
F	28.7	9.2	4.1	110/70	32	0.7	230	230	34	130	-ve	0.09	0.08	0.85	0.09	0.09	0.09	2
F	27.7	10.2	5.21	130/80	28	0.8	230	170	35	105	-ve	0.09	0.09	0.09	0.090	0.09	0.09	2
F	26.9	12.5	16.3	160/110	32	0.8	260	160	42	110	-ve	0.09	0.09	0.09	0.09	0.09	0.09	2
F	24.8	9.2	2.4	120/80	36	0.7	240	110	42	105	-ve	0.10	0.10	0.11	0.11	0.11	0.11	1
M	25.1	11.4	4.6	130/80	34	0.8	220	120	42	90	-ve	0.11	0.11	0.10	0.10	0.10	0.10	2
F	27.6	10.3	5.4	120/75	28	0.8	230	105	34	90	-ve	0.06	0.065	0.06	0.06	0.06	0.06	1
M	28.1	9.4	4.6	105/70	26	0.7	225	121	32	85	-ve	0.09	0.08	0.08	0.09	0.09	0.09	2
M	27	10.3	7.4	110/70	32	0.8	230	120	34	84	-ve	0.07	0.07	0.07	0.07	0.07	0.07	1
M	26.2	10.6	5.3	120/70	38	1.2	210	110	38	80	-ve	0.09	0.09	0.09	0.09	0.09	0.09	2

Group 3 the age of patient (55-64)year

sex	BMI	HbA_{1c}	CRP	BP	UREA	CR	CHOL	TG	HDL	LDL	PU	Lt Ic MIT	RT IC MIT	M IC MIT	LT CC MIT	RT CC MIT	M CC MIT	D
M	26.7	10.3	4.8	130/90	32	0.9	210	180	42	110	-ve	0.11	0.11	0.11	0.10	0.10	0.10	1
M	26.5	13.4	8.3	110/70	28	0.8	220	220	32	120	-ve	0.09	0.09	0.09	0.09	0.09	0.09	2
M	33.6	7.6	3.3	130/80	24	0.6	190	130	45	80	-ve	0.09	0.09	0.09	0.09	0.09	0.09	1
M	28.06	7.5	7.6	120/80	32	0.8	240	145	40	110	-ve	0.06	0.06	0.06	0.07	0.07	0.07	1
F	26.2	10.2	15.2	120/80	32	0.8	263	217	42	115	-ve	0.10	0.11	0.105	0.11	0.11	0.11	2
F	24.3	8.5	6.2	120/80	28	0.6	220	170	40	120	-ve	0.06	0.07	0.065	0.07	0.07	0.07	2
F	27.3	8.5	9.1	130/70	35	0.9	265	406	30	120	-ve	0.11	0.11	0.11	0.12	0.12	0.12	1
F	30.6	14.1	12	140/80	35	0.9	314	210	33	220	-ve	0.08	0.08	0.08	0.09	0.09	0.09	2
M	31.8	10.5	3.2	130/90	32	0.8	269	210	40	140	-ve	0.10	0.10	0.10	0.10	0.11	0.105	2
M	25.9	11.2	6	130/80	32	0.9	224	152	34	110	-ve	0.08	0.08	0.09	0.09	0.09	0.09	2
F	25.7	10.7	2	120/80	28	0.8	210	110	36	90	-ve	0.07	0.07	0.07	0.07	0.07	0.07	2
F	27.6	12.2	6.6	110/70	34	0.9	220	105	35	95	-ve	0.09	0.09	0.09	0.09	0.09	0.09	1
F	27.1	12.6	6.6	110/60	37	0.8	270	130	36	85	-ve	0.11	0.11	0.10	0.10	0.10	0.10	1
M	23.9	10.9	2.2	130/70	30	0.9	190	110	34	75	-ve	0.10	0.10	0.09	0.09	0.09	0.09	1
F	26.78	7.5	2.5	100/60	32	0.8	210	160	35	110	-ve	0.09	0.09	0.09	0.89	0.80	0.095	1
M	28.7	10.2	4.1	140/80	30.2	0.8	102	110	32	95	-ve	0.08	0.08	0.08	0.09	0.09	0.09	2
M	24.6	10.8	3.2	110/60	32	0.7	240	105	38	85	-ve	0.09	0.09	0.09	0.09	0.09	0.09	2
F	26.5	12.1	7.6	130/80	36	0.9	220	110	32	80	-ve	0.08	0.08	0.07	0.07	0.07	0.07	2

Group 4 the age of patient (65-75)year

sex	BMI	HbA_{1c}	CRP	BP	UREA	CR	CHOL	TG	HDL	LDL	PU	Lt Ic MIT	RT IC MIT	M IC MIT	LT CC MIT	RT CC MIT	M CC MIT	D
M	23.8	8.3	12.5	160/80	26	0.8	220	160	35	90	-ve	0.12	0.1	0.11	0.10	0.12	0.11	2
M	25.4	9.4	8.2	120/70	29	0.8	230	180	35	115	-ve	0.07	0.07	0.07	0.08	0.08	0.08	1
F	20.5	8.6	4.3	120/80	26	0.8	205	140	30	110	-ve	0.06	0.08	0.07	0.06	0.07	0.065	1
F	27.7	12.5	15.3	140/80	41	0.5	167	138	32	90	-ve	0.06	0.07	0.065	0.06	0.06	0.06	2

BMI, body mass index ;**HbA_{1C}**, hemoglobin A1c ;**CRP**, C-reactive protein ;**BP**, Blood pressure ;**CR**, Serum Creatinine; **CHOL**, cholesterol ; **TG**, Triglyceride ;**HDL**, High-density lipoprotein ;**LDL**, Low-density lipoprotein ;**PU**, protienurea ;**Lf**, left ;**RT**, right ;**IC**, internal carotid ; **CC**, common carotid ;**MIT**, intima-media thickness ;**M**, mean ;**D_1,** repaglinide ;**D_2**, glimepiride .

Result

In comparing different pairs of patients and as shown in the tables and in between drug 1(repaglinide) and drug 2 (glimepiride) and after 12 months of treatment and in different parameters. the reduction in the CIMT of left internal carotid with p value <0.0001 and it is a significant one ,the reduction in the CIMT of the right common carotid artery is more with the repaglidine with p value <0.0019 and it is a significant . the reduction in the level of HbA_{1c} more with rapiglinide still not a significant with p value 0.127 , the same for CPR with p

value 0.137 and LDL with p value 0.317 ,for TG p value 0.939 and for s. cholesterol p 0.445 all not a significant.

Table 1 Paired T test Drug 1(repaglinide) baseline and after 6 months

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	HbA_{1C} - HbA_{1C}6	2.52258	2.05341	.36880	1.76939	3.27578	6.840	30	.000
Pair 2	CRP - CRP6	1.91613	3.26058	.58562	.72014	3.11212	3.272	30	.003
Pair 3	Urea - Urea6	1.09677	3.96951	.71294	-.35925-	2.55280	1.538	30	.134
Pair 4	CR - CR6	.18710	1.08436	.19476	-.21065-	.58484	.961	30	.344
Pair 5	Choll - Choll6	26.70968	39.02580	7.00924	12.39490	41.02446	3.811	30	.001
Pair 6	Trig - Trig6	-6.41935-	79.44129	14.26808	-35.55865-	22.71994	-.450-	30	.656
Pair 7	HDL - HDL6	16.58065	37.34950	6.70817	2.88074	30.28055	2.472	30	.019
Pair 8	LDL - LDL6	-17.70968-	43.51796	7.81606	-33.67219-	-1.74716-	-2.266-	30	.031
Pair 9	LtICMIT - LtICMIT6	.00452	.00961	.00173	.00099	.00804	2.618	30	.014
Pair 10	RtICMIT - RtICMIT6	.00242	.01802	.00324	-.00419-	.00903	.747	30	.461
Pair 11	MICMIT - MICMIT6	.04468	.15708	.02821	-.01294-	.10230	1.584	30	.124
Pair 12	LtCCMIT - LtCCMIT6	.00748	.02344	.00421	-.00112-	.01608	1.777	30	.086
Pair 13	RtCCMIT - RtCCMIT6	.02613	.12917	.02320	-.02125-	.07351	1.126	30	.269
Pair 14	MCCMIT - MCCMIT6	-.02032-	.12747	.02289	-.06708-	.02643	-.888-	30	.382

Table 2 Paired T test Drug 1(repaglinide) between after 6 months and after 12 months

Pired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	$HbA_{1C}6$ - $HbA_{1C}12$	.47419	1.10694	.19881	.06817	.88022	2.385	30	.024
Pair 2	CRP6 - CRP12	.56452	1.82475	.32773	-.10481-	1.23384	1.722	30	.095
Pair 3	Urea6 - Urea12	-.06452-	2.59404	.46590	-1.01602-	.88698	-.138-	30	.891
Pair 4	CR6 - CR12	-6.08968-	33.96563	6.10041	-18.54837-	6.36901	-.998-	30	.326
Pair 5	Choll6 - Choll12	-2.32258-	21.30162	3.82588	-10.13608-	5.49092	-.607-	30	.548
Pair 6	Trig6 - Trig12	2.80000	24.89343	4.54490	-6.49536-	12.09536	.616	29	.543
Pair 7	HDL6 - HDL12	.51613	5.47644	.98360	-1.49265-	2.52490	.525	30	.604
Pair 8	LDL6 - LDL12	-22.74194-	139.92450	25.13118	-74.06665-	28.58278	-.905-	30	.373
Pair 9	LtICMIT6 - LtICMIC12	.00323	.01045	.00188	-.00061-	.00706	1.718	30	.096
Pair 10	RtICMIT6 - RtICMIC12	.00387	.01116	.00200	-.00022-	.00796	1.931	30	.063
Pair 11	MICMIT6 - MICMIT12	-.02113-	.14123	.02537	-.07293-	.03067	-.833-	30	.411
Pair 12	LtCCMIT6 - LtCCMIT12	.02348	.14741	.02647	-.03058-	.07755	.887	30	.382
Pair 13	RtCCMIT6 - RtCCMIT12	-.01484-	.10188	.01830	-.05221-	.02253	-.811-	30	.424
Pair 14	MCCMIT6 - MCCMIT12	.01129	.15962	.02867	-.04726-	.06984	.394	30	.696

Table 3 Paired T test Drug 1(repaglinide) between baseline and after 12 months

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	HbA_{1C} - HbA_{1C}12	2.99677	2.42274	.43514	2.10811	3.88544	6.887	30	.000
Pair 2	CRP - CRP12	2.48065	3.14212	.56434	1.32810	3.63319	4.396	30	.000
Pair 3	Urea - Urea12	1.03226	3.75485	.67439	-.34503-	2.40955	1.531	30	.136
Pair 4	CR - CR12	-5.90258-	34.03895	6.11358	-18.38817-	6.58301	-.965-	30	.342
Pair 5	Choll - Choll12	24.38710	50.51777	9.07326	5.85703	42.91716	2.688	30	.012
Pair 6	Trig - Trig12	-8.10000-	91.24516	16.65901	-42.17150-	25.97150	-.486-	29	.630
Pair 7	HDL - HDL12	17.09677	39.28389	7.05559	2.68733	31.50622	2.423	30	.022
Pair 8	LDL - LDL12	-40.45161-	146.75168	26.35738	-94.28056-	13.37734	-1.535-	30	.135
Pair 9	LtICMIT - LtICMIC12	.00774	.01087	.00195	.00376	.01173	3.967	30	.000
Pair 10	RtICMIT - RtICMIC12	.00629	.02074	.00372	-.00132-	.01390	1.689	30	.102
Pair 11	MICMIT - MICMIT12	.02355	.12801	.02299	-.02341-	.07050	1.024	30	.314
Pair 12	LtCCMIT - LtCCMIT12	.03097	.14871	.02671	-.02358-	.08552	1.159	30	.255
Pair 13	RtCCMIT - RtCCMIT12	.01129	.16939	.03042	-.05084-	.07342	.371	30	.713
Pair 14	MCCMIT - MCCMIT12	-.00903-	.08758	.01573	-.04116-	.02309	-.574-	30	.570

Table 4 Paired T test Drug 2 (glimepiride) baseline and after 6 months

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	HbA_{1C} - $HbA_{1C}6$	3.22581	1.56076	.28032	2.65331	3.79830	11.508	30	.000
Pair 2	CRP - CRP6	2.66333	6.41751	1.17167	.26699	5.05967	2.273	29	.031
Pair 3	Urea - Urea6	-.05806-	4.48678	.80585	-1.70383-	1.58770	-.072-	30	.943
Pair 4	CR - CR6	-.07000-	.18520	.03326	-.13793-	-.00207-	-2.104-	30	.044
Pair 5	Choll - Choll6	27.22581	39.97642	7.17998	12.56234	41.88927	3.792	30	.001
Pair 6	Trig - Trig6	-17.19355-	65.06787	11.68653	-41.06064-	6.67354	-1.471-	30	.152
Pair 7	HDL - HDL6	16.09677	35.56436	6.38755	3.05166	29.14189	2.520	30	.017
Pair 8	LDL - LDL6	-15.93548-	47.81418	8.58768	-33.47387-	1.60290	-1.856-	30	.073
Pair 9	LtICMIT - LtICMIT6	.01323	.02468	.00443	.00417	.02228	2.983	30	.006
Pair 10	RtICMIT - RtICMIT6	.00581	.00992	.00178	.00217	.00945	3.258	30	.003
Pair 11	MICMIT - MICMIT6	.06871	.19318	.03470	-.00215-	.13957	1.980	30	.057
Pair 12	LtCCMIT - LtCCMIT6	.00419	.01858	.00334	-.00262-	.01101	1.257	30	.219
Pair 13	RtCCMIT - RtCCMIT6	.00850	.00975	.00178	.00486	.01214	4.774	29	.000
Pair 14	MCCMIT - MCCMIT6	.00790	.00920	.00168	.00446	.01134	4.701	29	.000

Table 5 Paired t test drug 2 (glimepiride) between after 6 months and after 12 months

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	$HbA_{1C}6$ - $HbA_{1C}12$	.34194	.97015	.17424	-.01392-	.69779	1.962	30	.059
Pair 2	CRP6 - CRP12	1.40000	5.52930	1.00951	-.66467-	3.46467	1.387	29	.176
Pair 3	Urea6 - Urea12	.48387	3.43386	.61674	-.77568-	1.74342	.785	30	.439
Pair 4	CR6 - CR12	.01290	.13599	.02443	-.03698-	.06279	.528	30	.601
Pair 5	Choll6 - Choll12	6.29032	23.90843	4.29408	-2.47936-	15.06000	1.465	30	.153
Pair 6	Trig6 - Trig12	-3998.50000-	21907.31141	3999.70955	-12178.82452-	4181.82452	-1.000-	29	.326
Pair 7	HDL6 - HDL12	.41935	4.33416	.77844	-1.17043-	2.00914	.539	30	.594
Pair 8	LDL6 - LDL12	3.87097	28.00088	5.02911	-6.39984-	14.14177	.770	30	.447
Pair 9	LtICMIT6 - LtICMIC12	-.00194-	.02372	.00426	-.01064-	.00677	-.454-	30	.653
Pair 10	RtICMIT6 - RtICMIC12	.00387	.01116	.00200	-.00022-	.00796	1.931	30	.063
Pair 11	MICMIT6 - MICMIT12	.00435	.01250	.00224	-.00023-	.00894	1.940	30	.062
Pair 12	LtCCMIT6 - LtCCMIT12	.00419	.01089	.00196	.00020	.00819	2.145	30	.040
Pair 13	RtCCMIT6 - RtCCMIT12	.00300	.01119	.00204	-.00118-	.00718	1.469	29	.153
Pair 14	MCCMIT6 - MCCMIT12	-.01267-	.09082	.01658	-.04658-	.02125	-.764-	29	.451

Table 6 Paired t test Drug 2 (glimepiride) between baseline and after 12 months

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	HbA_{1C} - $HbA_{1C}12$	3.56774	1.82782	.32829	2.89729	4.23819	10.868	30	.000
Pair 2	CRP - CRP12	4.03871	4.83843	.86901	2.26396	5.81346	4.647	30	.000
Pair 3	Urea - Urea12	.42581	4.35362	.78193	-1.17111-	2.02273	.545	30	.590
Pair 4	CR - CR12	-.05710-	.19372	.03479	-.12815-	.01396	-1.641-	30	.111
Pair 5	Choll - Choll12	33.51613	42.63166	7.65687	17.87871	49.15355	4.377	30	.000
Pair 6	Trig - Trig12	17.517-	81.983	15.223	48.702	13.667	1.151	28	0.260
Pair 7	HDL - HDL12	16.51613	36.51746	6.55873	3.12142	29.91084	2.518	30	.017
Pair 8	LDL - LDL12	-12.06452-	54.99572	9.87752	-32.23711-	8.10808	-1.221-	30	.231
Pair 9	LtICMIT - LtICMIC12	.01129	.01118	.00201	.00719	.01539	5.624	30	.000
Pair 10	RtICMIT - RtICMIC12	.00968	.01140	.00205	.00550	.01386	4.728	30	.000
Pair 11	MICMIT - MICMIT12	.07306	.19509	.03504	.00151	.14462	2.085	30	.046
Pair 12	LtCCMIT - LtCCMIT12	.00839	.02035	.00365	.00092	.01585	2.295	30	.029
Pair 13	RtCCMIT - RtCCMIT12	.01306	.01716	.00308	.00677	.01936	4.239	30	.000
Pair 14	MCCMIT - MCCMIT12	-.00461-	.08913	.01601	-.03730-	.02808	-.288-	30	.775

Table 7 Differences between Drug 1(repaglinide) and Drug 2(glimepiride) groups regarding Age, Wt, Ht and BMI

dependent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	upper
Age	Equal variances assumed	.900	.346	-.812-	60	.420	-2.12903-	2.62313	-7.37608-	3.11801
	Equal variances not assumed			-.812-	58.158	.420	-2.12903-	2.62313	-7.37950-	3.12143
Wt	Equal variances assumed	1.722	.194	-1.149-	60	.255	-3.45161-	3.00505	-9.46260-	2.55938
	Equal variances not assumed			-1.149-	49.860	.256	-3.45161-	3.00505	-9.48785-	2.58463
Ht	Equal variances assumed	.297	.588	.823	60	.414	1.41935	1.72509	-2.03133-	4.87004
	Equal variances not assumed			.823	55.417	.414	1.41935	1.72509	-2.03721-	4.87592
BMI	Equal variances assumed	.049	.826	-1.765-	60	.083	-2.00839-	1.13783	-4.28439-	.26762
	Equal variances not assumed			-1.765-	55.055	.083	-2.00839-	1.13783	-4.28861-	.27183

Table 8 Independent T test differences between means of variables in Drug 1 and drug 2

Variables	Drug 1		Drug 2		P Value
	Mean	SD	Mean	SD	
HbA_{1C}	2.996	2.423	3.567	1.827	0.127
CRP	2.480	3.142	4.038	4.838	0.137
Urea	1.032	3.754	0.425	4.353	0.558
CR	5.902	34.038	0.057	0.193	0.343
Cho.	24.387	50.517	33.516	42.631	0.445
Trig.	8.100	91.245	17.517	81.983	0.939
HDL	17.096	39.283	16.516	36.517	0.952
LDL	40.451	146.751	12.064	54.995	0.317
Lt ICMIT	0.07	0.01	0.011	0.011	< 0.0001
RICMIT	0.006	0.020	0.0096	0.011	0.467
MICMIT	0.0235	0.128	0.073	0.195	0.237
LCCMIT	0.030	0.148	0.008	0.020	0.415
RCCMIT	0.011	0.169	0.013	0.017	0.0019
MCCMIT	0.009	0.087	0.004	0.089	0.823

Discussion

In our study compared repaglinide with glimepiride effect on atherosclerosis in patients presenting with NIDDM , we found that the use of repaglinide as compared with glimepiride is better in reduction the CIMT and the reduction was both with left internal carotid and the right common carotid with p value < 0.005 than glimepiride and the difference in benefit is a significant one. Although this reduction is associated with reduction in LDL level ,TG and the HbA_{1c} they were not a significant one so the changes in CIMT were independent to the changes in lipid profile in this study The duration of the study was one year and was of limited duration because of difficulty in our patients to stick to an appropriate time of test so we lost 8 patients during our study.

Repaglinide affect atherosclerosis in many ways, It affects the postprandial glucose level, Repaglinide interacts with the ATP-sensitive potassium channel so that causing

rapid postprandial hypoglycemia ,so the drug is given with each meal or immediately before to reduce meal-related glucose excursions.[23] in our study the reduction of HbA1Cwas more with Repaglinide but not significant(The aim in our study was not to reach glycemic control to level HbA1c less 6 to avoid hypoglycemic events) . Repaglinide also reduces endothelial dysfunctional in glucose manner.[24] Repaglinide modified liposomes targeted to activated platelet as potential vascular drug delivery system.[15] In a study designed on hypercholestremic rabbits ,it was found that both glimepiride and repaglinide reduced the atherosclerosis progression by interfering both with inflammatory and oxidative pathways as treatment with both did show significant effect on lipid parameters compare with induced treated rabbits. (this also seen in our study) also it showed significantly reduced elevation in CRP, IL-6,TNF-alpha[15]. In another study it was found that glimepiride prevent development of aortic atherosclerosis in fat fed rabbits, underlining mechanism was explained by inhibition of endothelial cell-mediated LDL oxidation [14]. It was also shown that glimepiride treatment enhances the biosynthesis of nitric mono oxide antioxidant[14]. Both repaglinide and glimepiride induced atherosclerosis protection actions by suppression of inflammation and oxidative stress.[26] The major advantage of repaglinide over glimepiride is their rapid and relatively short duration of action, which may attenuate postprandial glucose excursions and reduce the risk of fasting hypoglycemia.[25]

In our opinion we may get more benefit with extension the duration of the study and to see the effect on cardiovascular risk . We used both drugs and tried not to produce the hypoglycemic events. The age of the patients was 35-75 years(mean 53years) and we tried to avoid the older age patients so decreased the complication .The aim was not to reach glycemic control to level HbA1c less 6 to avoid hypoglycemic events. One interesting action of repaglinide is by shutting down the ATP-dependent potassium channels in the membrane of beta cell of islet of the pancreas stimulating Calcium influx and induces secretion of insulin and this may explain its better CIMT reduction.[26] It was found that intensive therapy for DM for 6 years decreased the progression of CIMT . Offer best control of blood sugar after pancreatic islet transplantation showed significant reduction in CIMT[19]. The median duration of diabetes in the study was 10 years approximately 35% of them had previous CVD ,the trial concluded that intensive glucose lowering produces no benefit in term of CVD risk reduction and even produces harm in high risk patients with type 2[22]. This was explained by more hypoglycemic events and in special old age patients included in the study. It seems that this is related to changes in lipid profile of the patients .The action to control cardiovascular risk (ACCORD) was designed to assess the impact of tight blood sugar control on CVD events in subjects with type 2DM. There was suggestion that patients who did not have a cardiovascular events before randomized and who had a base line of HbA1c of 8% or less had fewer fatal or nonfatal cardiovascular events with intensive control than with standard control. It was shown that reduction in the postprandial hyperglycemia In type 2 DM diabetic patients is associated with much reduction In atherosclerosis and in CIMT reduction[18]. This last explanation in (ACCORD) study put the Repaglinide better than glimepiride in CIMT reduction as it causes more

postprandial decrease in glucose level.[26]

Conclusions and Recommendations

Repaglinide is better than glimepiride in reduction the CIMT and we need to know the best dose of the drug needed to achieve the best respond and that is by use different dose study program and to for longer duration.

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