Effect of COX-2 Inhibitors Selectivity on Lipid Profile in Hyperlipidemic and Normolipidemic Type 2 Diabetics

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Abstract

Development of NSAIDS based on inhibiting cyclooxygenase activity. However, the different physiological consequences arrised by appearance of new drugs with different selectivity to COX-2 enzyme upon their administration with their relevant affects on some cardiovascular risk factors. To study the potential effects of relatively diclofenac and highly specific celecoxib COX-2 inhibitors on lipid profile and serum C-reactive protein in type 2 diabetes, whom have hyperlipidemia to be compared by their effects with normolipidemic patients. A total number of 34 type 2 diabetics (14 normolipidemics and 20 hyperlipidemics) treated with either diclofenac 100mg/day or celecoxib 200mg/day for eight weeks. Analysis of results indicated that diclofenac increased serum triglycerides (TG) whereas; celecoxib group exerted a significant reduction in total cholesterol (TC), triglycerides (TG) levels in hyperlipidemic patients. Normolipidemic diabetics showed a significant elevation in serum total cholesterol, triglycerides and low density lipoprotein-cholesterol (LDL) with significant reduction in high density lipoprotein-cholesterol (HDL) in those treated with diclofenac , whilst those treated with celecoxib exhibited no modification of serum lipids. The results of the present study indicated that the net effect of treatment of hyperlipidemic type 2 diabetics by diclofenac was mostly qualitative as indicated by elevated TG/HDL ratio, to be a marker of atherogenic- small dense LDL particles in diabetics, whereas celecoxib exerted no such effect in this group but produced a beneficial reduction in LDL/HDL ratio. Meanwhile, diclofenac in normolipidemic diabetics exert a significant qualitative and quantitative modulation of their serum lipid components presented by net elevation in both LDL/HDL and TG/HDL ratios. As a conclusion the administration of relatively selective COX-2 inhibitors (diclofenac) to normolipidemic type 2 diabetics could adversely affect lipid metabolism by producing undesirable qualitative as well as , quantitative changes in serum lipid components, more than that observed in the hyperlipidemic diabetics.

Key Words: Diabetes, lipid profile, cox-2 selectivity

الخلاصة

لغرض دراسة تاثير مثبطات السايكلواوكسجنيس التامة والنسبية على مستوى الدهون في الدم عند مرضى السكري من النوع الثاني ذو التركيز العالي و الطبيعي للدهون وكذلك دراسة تاثير هذه الادوية على تركيز البروتين الفعالC في الدم عند هؤلاء المرضى . فان ٣٤ مريضا قد شاركوا بهذه الدراسة قد تم علاجهم اما بالدايكلوفيناك (١٠٠ ملغم يوميا) او السيليكوكسيب (٢٠٠ ملغم يوميا) لمدة ٨ اسابيع بعد تحليل النتائج وجد ان الدايكلوفيناك يزيد من تركيزثلاثي الغلسيريد ويؤدي الى زيادة نسبة(ثلاثي الغلسيريد / الدهون عالية الكثافة) في الدم بينما السيليكوكسيب يقلل من تراكيزكل من الكولستيرول , ثلاثي الغلسيريد ويؤدي الى نقصان في نسبـــة (الدهون واطئة الكثافة/ الدهون عالية الكثافة) عند مرضى السكر ذو التركيز العالي للدهون . اما عند مرضى السكر ذو التركيز الطبيعي للدهون فان الدايكلوفيناك يؤدي الى زيادة تراكيز كل من الكولستيرول , ثلاثي الغلسيريد والدهون واطئة الكثافة مع نقصان في تراكيز الدهون عالية الكثافة وكذلك يؤدي الى زيادة ملحوظة في نسب الدهون في الدم (نسبة الدهون واطئة الكثافة/ الدهون عالية الكثافة) وكذلك (نسبة ثلاثي الغلسيريد /الدهون عالية الكثافة) . بينما السيليكوكسيب لا يؤثر بشكل ملحوظ على تراكيز الدهون عند هؤلاء المرضى. وكذلك وجد من خلال الدراسة بان كلا العلاجين يؤديان الى نقصان ملحوظ في تركيزالبروتين الفعال C في الدم .لذلك فان اعطاء الدايكلوفيناك(والذي يعتبر مثبط نسبي لانزيم السايكلواوكسجنيس) الى مرضى السكر ذو التركيز الطبيعي للدهون قد يؤدي الى زيادة غير مفضلة كمياً ونوعياً في مستوى الدهون في الدم اكثر مما هو ملاحظ عند المرضى ذوي التركيز العالي للدهون.

Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Chronic hyperglycemia is associated with long – term failure of various organs, including small and large blood vessels [(1)] and peripheral neuropathy among the commonest complications in those patients.Neuropathy accurse in 60-70% of diabetics, where excess sugar can injure the walls of the tinny blood vessels that nourish the nerves especially in the legs leading to tingling, numbness, burning or pain sensation in the fingers [(2)].

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Treatment of diabetic neuropathy include primary prevention, management of early symptoms and relief of pain by drugs such as tricyclic antidepressant (TCA), analgesics and anticonvulsant therapy.[3] Meanwhile arthritis (joints inflammation) that causes pain and swelling due to damage in joints and connective tissues could be presented as osteoarthritis (OA) or rheumatic arthritis (RA) [4]. Osteoarthritis:-also known degenerative joint disease, this form of arthritis is usually limited affecting only the joints and is more painful later in the day. It's thought to be caused by defect in cartilage that results in bone destruction.[5] Rheumatic arthritis: - can affect most of the joints of the body and is associated with permanent morning stiffness and swelling, it can involve internal organs such as heart and lunges**.** [5] Because osteoarthritis and rheumatoid arthritis are so common so many people with these disorders could also have diabetes mellitus , Diabetic patients also has specific musculoskeletal disorders that caused by `diabetes─ neuropathy (nerve involvement) , arthropathies (disorder of joints and connective tissues) and problems with skin , tendons and muscle [5]The most common therapy utilized to control arthritis pain in those patients are the Non steroidal anti- inflammatory drugs (NSAIDS) which permit their action by inhibiting cyclooxygenase enzymeCox exists as two isoforms; Cox- 1 which is housekeeping enzyme and mediates physiological responses like (cytoprotection of stomach, platelet aggregation, vascular homeostasis and kidney functions). While COX-2 is mainly expressed by cells that are involved in inflammation like macrophage and monocyte**.** [6] However, four categories of COX inhibitors have been proposed [7, 8]

1- Selective COX-1 inhibitors: - these agents inhibit Cox-1 activity without any measurable effect on Cox-2 activity such as aspirin

2- Non selective COX inhibitors: - these agents demonstrate no meaningful biologic or clinical differences in the inhibition of Cox-1 versus Cox-2 activity like Ibuprofen, Naproxen and Indomethacin

3- Relaively Selective COX-2 inhibitors: - these drugs have analgesic and anti-inflammatory at doses that cause inhibition of Cox-2 butless inhibition of Cox-1 such as Diclofenac, Meloxicam and Nimesulide.

4- Highly selective COX-2 inhibitors: - inhibit the Cox-2 isoform but have no effect on Cox-1 isoform like Celecoxib and Rofecoxib

Cox-2 inhibitors can adversely affect the cardiovascular system because they don't inhibit Cox-1 derived ThromboxanA2(TXA2) which act as a vasoconstrictor and stimulates platelet aggregation. But prevent Cox-2 derived prostacycline (PGI_2) production which is a vasodilator with a potent inhibition of platelet aggregation, activation and adhesion of leukocytes and accumulation of cholesterol in vascular cells, [9, 10]. i.e. PGI2 act as endogenous antilipidemic agent Thus the cardiovascular effect of TXA2 would be expected to be exaggerated as the PGI_2 was known to act as a general retrain to any recognized stimulus to platelet activation. Deletion of the PGI_2 receptor inositol phosphate (IP), like Cox-2 inhibition elevates blood pressure and augment the pressure response to dietary sodium. Meanwhile variation in other endogenous mediators such as NO, could be expected to modulate the impact of Cox-2 inhibition on cardiovascular function. Thus, suppression of Cox-2 dependent PGI2 formation can both augment the response to thrombotic and hypertensive stimuli and initiate and accelerate atherogenesis [10] The effect of selectivity to Cox-2 enzymes on the various components of lipid profile were studied in both normo- and hyperlipidemic(having total cholesterol ≥ 5.18mmol/l and/or triglycerides ≥ 1.69 mmol/l) diabetes with arthritis.

Materials and Methods

This study was carried out at the National center for Diabetes─ Al Mustansiria University, for the period from November / 2007 to July / 2008 The study included 34 patients with type 2 diabetes mellitus (14 normolipidemic and 20 hyperlipidemic) aging between (40 and56) years old with duration of diabetes from (3 to 6) years, having osteoarthritis or rheumatoid arthritis, under the supervision of a senior physicion of the center.All the patients have type 2 DM using Aspirin therapy and maintained on oral hypoglycemic agents (Glibenclamide and / or Metformine) before and during the study period and not receiving insulin therapy . All pregnant , breast feeding women hypertensive , and patients with cardiovascular diseases were excluded, Also patients with any history of gastrointestinal tract problem like peptic ulcer and duodenal ulcer,or having allergy to sulfa drugs and patients who used hypolipidemic drugs were excluded . All the patients received medical advice to keep their medications and diets under control throughout

the study. In addition to diabetic patients sixteen healthy subjects were included in the study as a control, with age and sex matching that of the patients .The selected subjects were categorized according to their therapy to be received as follows:

Group 1: included 20 hyperlipidemic diabetic patients(13 females and 7 males) with arthritis (13) of them were treated with celecoxib 200 mg/day taken as a single dose for 8 weeks**,** while the reminder (7) were treated with diclofenac 100mg/day after meals as a single dose for 8 weeks **.**

Group 2: included 14 normolipidemic diabetic patients (10 females and 4 males) with arthritis (7) of them treated with celecoxib 200 mg/day and (7) treated with diclofenac 100 mg/day after meal as a single dose for 8 weeks period.

Group 3: included sixteen apparently healthy subjects (9 females and 7 males) considered as the control group Fasting venous blood sample were drawn from each patient at baseline and after 8 weeks of receiving either celecoxib or diclofenac therapy. Then serum was separated and stored frozen for the performance the enzymatic assays of Total cholesterol (TC) [(11)], Triglycerides (TG) [(12)], and High density lipoprotein-cholesterol (HDL-c) [(13)] . Low density lipoprotein-cholesterol (LDL-c) was determined according to Freiwald equation [(14)], Plasma hs-CRP was measured by Votila method based on ELISA technique [(15)].

Results

Table (1) shows that diclofenac causes a significant increase in serum TG level (% change = +43.74) in hyperelipidemic diabetic patients (Figure 2) without significant changes in serum TC, HDL-c, and LDL-c levels , while celecoxib produced significant decline in serum TC and TG (% changes are – 8.13, ─19.72) respectively (figures 1, 2) without significant changes in serum HDL-c and LDL-c level. normolipidemic patients recieved diclofenac showed a significant increase in serum TC, TG and LDL-c with significant decline in serum HDL-c level (% changes = + 12.51, + 21.34, + 27.21, - 11.72) respectively (figures 1,2,4,3). While celecoxib produced non significant changes in serum TC, TG, HDL-c and LDL-c levels. Table (2) shows that in hyperlipidemic diabetic patients diclofenac caused a significant increase in serum TG/HDL-c ratio % change +73.87 (figure 6) without significant difference in serum LDL-c/HDL-c ratio. While, celecoxib showed a significant decline in serum LDL-c/HDL-c ratio (% change -16.46 figure (5) without a significant effect on serum TG/HDL-c ratio .In normolipidemic patients diclofenac produce significant increase in both LDL-c/HDL-c and TG/HDL-c ratios (% changes =+46.79, 39.02 , respectively (figures 5, 6) .wherase, celecoxib produce no significant changes in those ratios.

Table(1): Effect of treatment with diclofenac or celecoxib on lipid profile in normolipidemic and hyperlipidemic type 2 diabetic patients

Group	Type of therapy	Duration of therapy	Total cholesterol (TC)	Triglyceride (TG)	High density lipoprotein (HDL)	Low density lipoprotein (LDL)
Control N=16			4.52± 0.22	1.22± 0.06	1.46± 0.05	2.50 ± 0.2
hyperlipidemic N= 20	Diclofenac N= 7	Baseline After 8 weeks	6.68± 0.43*a 7.60 ± 0.68*a	2.05± 0.35*a 2.94± 0.54*b	1.49 ± 0.09a 1.34±0.11a	4.25± o.52*a 4.96 ±0.80*a
	Celecoxib N= 13	Baseline After 8 weeks	6.66± 0.37*a 6.12±0.33*b	1.94±0.24*a 1.56±0.15*b	1.48±0.10a 1.57±0.07a	4.30±0.36*a 3.84±0.37*a
normolipidemc N= 14	Diclofenac N= 7	Baseline After 8 weeks	4.51±0.20a 5.07±0.34b	1.15±0.10a 1.40±0.13b	1.62±0.08a 1.43±0.11b	2.36±0.23a 3.00±0.36b
	Celecoxib N= 7	Baseline After 8 weeks	4.42±0.26a 5.15±0.52a	1.44±0.06*a 1.32±0.10a	1.55±0.09a 1.68±0.11a	2.20±0.25a 2.86±0.52a

Data are presented as mean ± SEM (mmol / L)

N = number of patients

*P < 0.05 with respect to control group

Non identical superscript (a , b) within the same drug group represent significant difference , P < 0.05

Table (2): Effect of treatment with diclofenac or celecoxib on lipid ratios (LDL/HDL) , (TG/HDL) in normolipidemic and hyperlipidemic type 2diabetics

Group	Type of therapy	Duration of therapy	LDL/HDL	TG/HDL
Control N=16			1.72± 0.13	0.86± 0.06
Hyperlipidemic N= 20	Diclofenac N=7	Baseline After 8 weeks	2.95± 0.44*a 3.88± 0.80*a	1.41± 0.25*a 2.45± 0.61*b
	Celecoxib N=13	Baseline After 8 weeks	3.04± 0.31*a 2.54± 0.27*b	1.47±0.28*a 1.03± 0.15a
Normolipidemic N= 14	Diclofenac N=7	Baseline After 8 weeks	1.51± 0.18a 2.21± 0.34b	0.71± 0.05a 0.99±0.09 b
	Celecoxib N=7	Baseline After 8 weeks	1.46± 0.21a 1.77± 0.35a	0.94±0.05a 0.82 ±0.10a

Data are presented as mean ± SEM
N = number of patients
*P < 0.05 with respect to control group
Non identical superscript (a , b) within the same drug group represent significant difference , P < 0.05

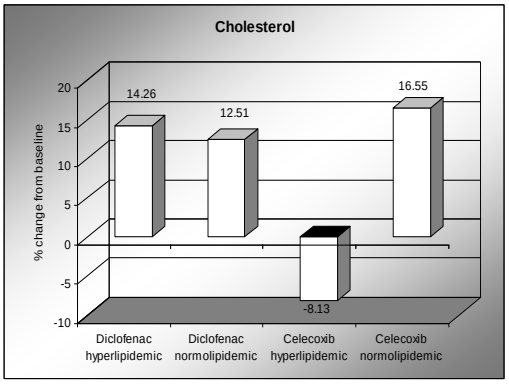

Figure (1): - The % changes in serum total cholesterol concentration from baseline value after 8weeks treatment with diclofenac or celecoxib in hyperlipidemic and normolipidemic type 2 diabetic patients

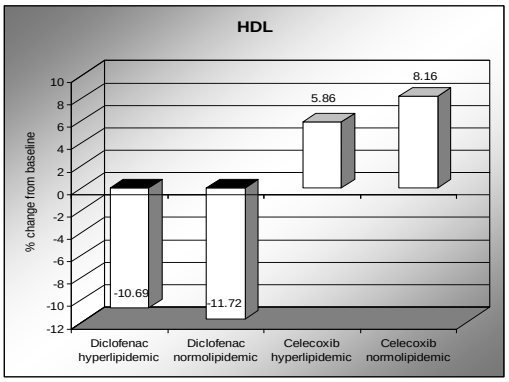

Figure (3):- The % changes in serum HDL-cholesterol concentration from baseline valuet after 8weeks treatment with diclofenac or celecoxib in hyperlipidemic and normolipidemic type 2 diabetic patients

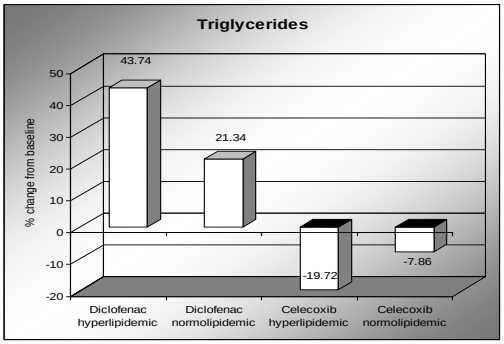

Figure (2) :- The % changes in serum triglycerides concentration frombaseline value after 8weeks treatment with diclofenac or celecoxib in hyperlipidemic and normolipidemic type 2 diabetic patients

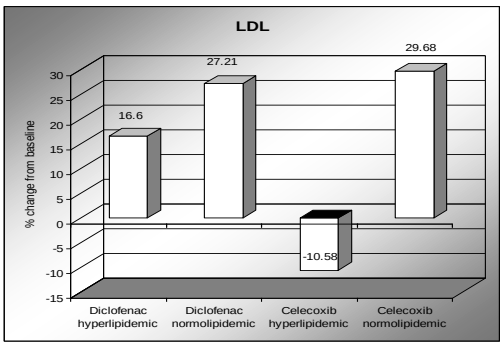

Figure (4) : -The % changes in serum LDL-cholesterol concentration from baseline value after 8weeks treatment with diclofenac or celecoxibin hyperlipidemic and normolipidemic type 2 diabetic patients

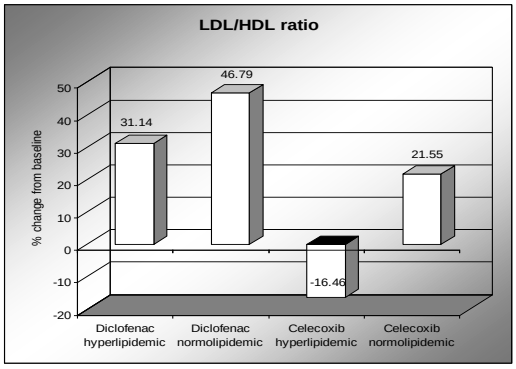

Figure (5):-The % changes in serum LDL/HDL ratio concentration from baseline value after 8weeks treatment with diclofenac or celecoxib in hyperlipidemic and normolipidemic type 2 diabetic patients

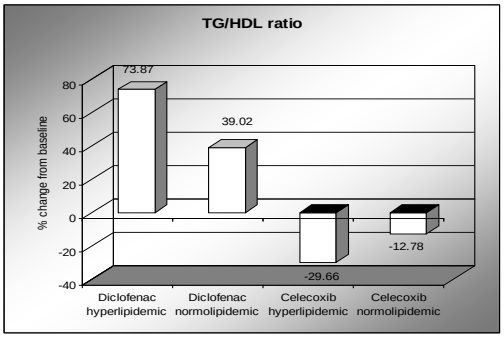

Figure (6): - % change in serum TG/HDL ratio concentration from baseline value after 8weeks treatment with diclofenac or celecoxib in hyperlipidemic and normolipidemic type 2 diabetic patients

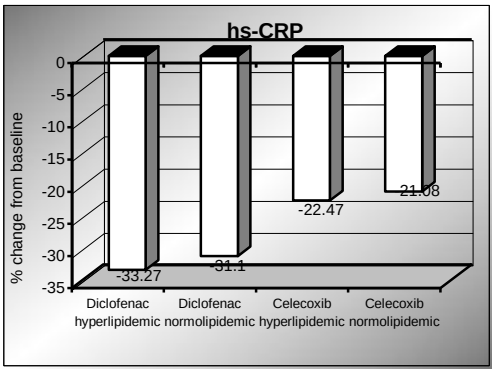

Figure (7): - The % change in serum hs-CRP concentration from baseline value after 8 weeks treatment with diclofenac or celecoxib in hyperlipidemic and normolipidemic type 2 diabetic patients

Discussion

Arthritis and diabetes are both common conditions that affects large population, the musculoskeletal system can be affected in diabetes , leading to several pathological conditions such as arthritis [(5)] In hyperlipidemic diabetics, the diclofenac produced a significant increase in serum triglycerides and exerts a qualitative changes in their serum lipid components (increase TG/HDL) .while hyperlipidemic diabetic patients treated with celecoxib showed a significant decline in serum total cholesterol level and producing a significant decline in LDL/HDL ratio (i.e. has beneficial quantitative effect on serum lipid ratio). These results agree with another study which reported that celecoxb decrease fat deposition in rats fed a high- fat diet and that celecoxib could lower serum and hepatic lipids (usually TG) in rats by mechanism not related to Cox-2 inhibition but by inhibition of fatty acid synthase expression which is a central enzyme in lipogenesis. [(16)] Meanwhile other reports shown that Cox-2 has anti –atherogenic activity so that rats given a selective Cox-2 inhibitors (Rofecoxib) had increased cardiovascular side effects not only due to the increase TXA2 in circulation(as Cox2 inhibitors don't inhibit Cox-1 derived ThromboxanA2) but also Cox-2 deficiency resulted in accumulation of lipids in circulation ,and animals that given selective Cox-2 inhibitors have higher serum cholesterol , TG, and HDL than animals not given Cox-2 inhibitors [(17).] Similarly other study applied on arthritis patients treated with celecoxib (selective Cox-2 inhibitors) and meloxicam (non selective Cox-2 inhibitors) had shown that celecoxib treated patients have higher serum cholesterol, TG and HDL than the control group, while those treated with meloxicam have higher serum cholesterol, TG but lower HDL than the control, indicating that selective Cox2 inhibitors increased the cardiovascular risk markers in those patients [(18)] Many reports study the effect of different types of NSAIDS on lipid profile had shown that NSAIDS (among these drugs flufenamic acid , ibuprofen ,acetaminophen, indomethacin and acetysalicylic acid) could lower serum cholesterol level in normocholesterolemic subjects because these drugs enhance LDL catabolism due to increased synthesis of mRNA of LDL receptors proteins [(19).] Also a study carried on animals had demonstrated that diclofenac therapy could lower serum lipids, oxidized LDL, serum antioxidant defenses and markers of oxidative stress in rats Receiving diclofenac for 28 days [(20)].We also studied the effect of celecoxib and diclofenac on hs-CRP level which is a cut phase protein produced by the liver and rise significantly in response to

injury, infection, and other inflammatory conditions and considered as a good marker of cardiovascular events [21]. Results analysis had shown that both drugs lowered serum hs-CRP in both hyper and normolipidemic diabetics to similar degree with a greater effect produced by diclofenac. This agree with other study carried on humans and shown that when celecoxib given to patients with coronary artery disease for 2 weeks causes significant lowering in serum hs- CRP and oxidized LDL levels as compared with placebo [22].Another study involve diclofenac demonstrate that diclofenac administration to patients undergoing major urological surgery was associated with lower leukocyte count, CRP concentration and temperature than the placebo group indicating that diclofenac may have anti-inflammatory role in major surgery[23].

Conclusion

The administration of relatively selective Cox-2 inhibiters (diclofenac) to normolipidemic type 2 diabetic could adversely effect lipid metabolism by producing qualitative and quantitative changes in serum lipid components more than that observed in hyperlipidemic patients.

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