

**A Comparative Study of The Effect of Selectivity of COX-2 Inhibition
(Meloxicam & Celecoxib) on Some Cardiovascular Risk Markers in
Patients With Rheumatoid Arthritis**

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الخلاصة

مقدمة: ان الإنزيمات المصنعة للبروستاغلاندين (السايلووكسيجينات) هي الانزيمات التي تساعد على تحويل حامض الراكيدونيك الى سلسلة من المركبات والتي تنتهي بالبروستاغلاندينات والتي هي مركبات محفزة لعدد من الفعاليات الحيوية الفسلجية في الكثير من اجهزة الجسم ومن ضمنها جهازي الدوران والجهاز البولي. في الحالات الطبيعية هناك موازنة بين تأثيرات الثرومبوكسان أ2 المشتق من سايلووكسيجيناز 1 والذي يعمل كمحفز للصفائح الدموية المساعدة على تخثر الدم في حين تكون التأثيرات الحامية للقلب المضادة للخرثرة للبروستايلين المشتق من انزيم السايلووكسيجيناز 2 وعليه فان تثبيط البروستايلين المشتق من السايلووكسيجيني -2 سيزيد من التأثيرات الوعائية القلبية للثرومبوكسان أ. ان الادوية المضادة للالتهابات غير الستيرويدية (التقليدية) تثبط تكوين كلا البروستاغلاندينان (بروستايلين و ثرومبوكسان أ2), وعليه فانها تحافظ على هذا التوازن طبيعيا او قرب الطبيعي.

الهدف: تتضمن هذه الدراسة المقارنة بين تأثير كل من المثبط الخاص بالسايلووكسيجيناز 2 (عقار السيليكوكسيب) و المثبط النسبي لنفس الانزيم (ميلوكسيكام) على بعض عوامل الخطورة للاصابة بامراض القلب في مرضى التهاب المفاصل .

طريقة العمل: تم اختيار ست وثلاثون مريضا لديهم إصابة بالتهاب المفاصل الالتهابي بمعدل أعمار يتراوح بين 30-60 سنة (48 ± 9,72). اضافة الى اثني عشر من الأشخاص الأصحاء ظاهريا كمجموعة قياسية. تم قياس البروتين الفعال (س) عالي الحساسية و انزيم الكرياتين كينيز و اليوريا و الكرياتينين و مستوى الدهون. تم تقسيم المرضى حسب العلاج اما بالسيليكوكسيب (400 ملغم يوميا) او بالميلوكسيكام (15 ملغم يوميا) لمدة ثلاثة اشهر.

النتائج: من خلال دراستنا أثبتت النتائج بان مثبط الكوكس التام (سيليكوكسيب) لم يكن مختلفا بشكل هام عن مثبط الكوكس النسبي (الميلوكسيكام) في التأثير بالعوامل المدروسة . حيث ان كلاهما قلل وبشكل هام (البروتين الفعال س عالي الحساسية). وكذلك كلاهما سبب زيادة في الكوليستيرول الكلي في المصل,

البروتينات الدهنية واطئة الكثافة ونسبة البروتينات الدهنية واطئة الكثافة الى البروتينات الدهنية عالية الكثافة عما كانت عليه قبل العلاج. كلا العقارين استطاعا ان يقللا معدل التناضح الكبيبي والمتمثلة برفع مستويات اليوريا في الدم. ومن الاختلافات الناتجة هي ان الميلوكسيكام رفع انزيم الكرياتينين كابينيز في المصل. بينما لم يعمل ذلك السيليكوكسيب.

الاستنتاج: وعليه فأن درجة انتقائية تثبيط انزيم السايكلو اوكسجيناز -2 هو ليس العامل الاساسي الذي يحدد زيادة عوامل الخطورة القلبية للمرضى الذين يستخدمون هذا العلاج . حيث ان العلاج بالميلوكسيكام يمكن ان يشكل خطورة اكبر لدى المرضى المعالجين به من السيليكوكسيب وذلك من خلال تسببه بزيادة فعالية انزيم الكرياتينين كابينيز في المصل .

Abstract

Background: Prostaglandin G/H Synthases (Cyclooxygenases) are enzymes that catalyze the conversion of arachidonic acid to a series of compounds ending in prostaglandins, endogenous compounds triggering many biological & physiological events in many systems including circulatory & renal systems. The normal balance between Cox-1 derived thromboxane A₂ (TXA₂) which acts as a platelet activator enhancing thrombosis, & the antithrombotic cardioprotective effects of prostacyclin (PGI₂) which is produced through Cox-2 activity. Thus inhibition of Cox-2 derived PGI₂ will exaggerate the cardiovascular effects of TXA₂. Cyclooxygenase - 2 (Cox-2) inhibitors have different odds on cardiovascular risk factors through selectivity to that enzyme that could play a role in their pharmacological action.

Objective: Our study includes a comparison between the effects of the purely cox-2 selective inhibitor (Celecoxib), and the relatively Cox-2 selective inhibitor (Meloxicam) on some cardiovascular risk markers in patients suffering from rheumatoid arthritis.

Materials & Methods: Thirty –six patients were selected as having rheumatoid arthritis (RA) with age range of 30-60 years (48±9.72), in addition to a group of normal subjects (12) were included as a control group Specific biochemical investigations based on measuring highly sensitive kit for serum C – reactive protein (hs-CRP), serum creatine kinase(CK), serum aspartate aminotransferase(AST), serum urea, serum creatinine, and serum lipid profile. The patients were treated with celecoxib 400mg/day or with meloxicam 15mg/day for 3 months period.

Results: Both drugs were able to reduce (significantly) the highly sensitive C-reactive protein and increase serum total cholesterol, Low Density Lipoprotein /High Density Lipoprotein (LDL/HDL) ratio as compared pretreatment values. Both drugs have nearly the same effects on renal function presented by

decreasing glomerular filtration rate (GFR) as indicated by elevating serum urea levels.

Conclusion: The selectivity of COX2 inhibition is not the major character that could be correlated with cardiovascular events related to their administration. Since, meloxicam could aggravate some cardiovascular risk factors more than celecoxib does, as presented a significant increment in serum CK activity.

Keywords: Meloxicam, Celecoxib, Cardiovascular risk markers, CRP, Rheumatoid arthritis.

Introduction

Cyclooxygenase (Cox) is an enzyme that is responsible for formation of important biological mediators called prostanoids (including prostaglandins, prostacyclin and thromboxane). Cox converts arachidonic acid (AA, an ω -6 essential fatty acid) to prostaglandin H₂ (PGH₂), the precursor of the series-2 prostanoids. The enzyme contains two active sites: a cyclooxygenase site, where arachidonic acid is converted into the hydroperoxy endoperoxide prostaglandin-G₂ (PGG₂), and a heme with peroxidase activity, responsible for the reduction of PGG₂ to PGH₂.

Currently three Cox isoenzymes are known Cox-1, Cox-2 and Cox-3. Cox-3 is a splice variant of Cox-1 which retains intron one and has a frame shift mutation, thus some prefer the name Cox-1b or Cox-1 variant (Cox-1v) ^[1]. In terms of their molecular biology, Cox-1 and Cox-2 are of similar molecular weight (approximately 70 and 72 kDa, respectively), and having 65% amino acid sequence homology and near-identical catalytic sites. The most significant difference between the isoenzymes, which allows for selective inhibition, is the substitution of isoleucine at position 523 in Cox-1 with valine in Cox-2. The relatively smaller Val₅₂₃ residue in Cox-2 allows access to a hydrophobic side-pocket in the enzyme (while Ile₅₂₃ sterically hinders). Drug molecules, such as DuP-697 and the coxibs derived from it, bind to this alternative site and are considered to be selective inhibitors of Cox-2 ^[2].

A 2006 analysis of 138 randomised trials and almost 150 000 participants, showed that selective Cox-2 inhibitors are associated with a moderately increased risk of vascular events, mainly due to a two fold increased risk of myocardial infarction ^[3], and also that high dose regimens of some traditional NSAIDs such as diclofenac and ibuprofen are associated with a similar increase in risk of vascular events ^[4,5].

Some studies have evaluated several acute phase proteins as potential markers for cardiovascular risk assessment, and there are several evidences that C-reactive protein (CRP) is a reliable predictor of acute coronary syndrome risk ^[6, 7]. A mild elevation of baseline levels of hs-CRP among apparently healthy individuals is associated with higher long-term risk for future cardiovascular

events. This predictive capacity offers patients the ability to receive treatment to reduce inflammation and thus, their risk ^[8, 9].

Celecoxib is a NSAID reported to be a selective inhibitor of cyclooxygenase-2. It is used in the treatment of rheumatoid arthritis and osteoarthritis and in the adjunctive treatment of adenomatous colorectal polyps ^[10, 11, 12]. Celecoxib is also used in the management of acute pain and dysmenorrhoea ^[13,14].

Meloxicam has been shown to have a Cox-1: Cox-2 selectivity of 3.77:1 ^[15]. Its selectivity for Cox-2 is dose dependent and is reduced at higher doses. Therefore meloxicam has been labeled a "preferential" inhibitor instead of a "selective" inhibitor of Cox-2 ^[16].

This study was designed to estimate the effect of treatment of patients having arthritis with either Meloxicam (relatively Cox-2 inhibitor) or celecoxib (absolutely Cox-2 inhibitor), on some biomarkers of cardiovascular risk (hs - CRP, AST, CK, and LDL/HDL) in addition to their effects on kidney performance.

Materials and Methods

The study was carried out at Al-Basrah General Hospital from December 2006 until August 2007. Sixty patients with RA were selected to participate in this study under the supervision of an orthopedic. Only 36 patients completed the courses of the study, twelve patients of them were males (33.33%), and 24 patients of them were females (67.66%).

Age ranged between 30 & 60 years [mean \pm Standard Deviation (48 \pm 9.72)]. Patients were treated as follows :-group 1: Included 12 patients treated with meloxicam (mobic) 15 mg/day, to be taken at night in single daily dose for 3 months.-group 2: Included 24 patients treated with celecoxib 400mg/day to be taken after meals in two divided doses for 3 months.

Blood specimens were collected from patients, then serum separated to be used for measuring the following variables: hs CRP ^[17], TC ^[18], TG ^[19], HDL-C ^[20], LDL-C ^[21], urea ^[22], creatinine ^[23], AST ^[24], CK-total ^[25].

The statistical analysis of our results included, -Mean \pm Standard error of the mean, students T – test (was used to examine the difference in the mean of parameters tested between studies groups).The results of analysis with (P) values <0.05 was considered significant ^[26].

Results

Analysis of data showed that patients treated with meloxicam for 3 months produced a significant increase (p<0.05) in total serum cholesterol values as compared to that of pretreatment values (percentage change was + 4%) figure-1. Meanwhile, patients treated with celecoxib for 3 months showed also a

significant increase ($p < 0.05$) in total serum cholesterol values (percentage change was +8.87%).

Figure -2 presents that patients treated with meloxicam for 3 months have no significant difference ($p > 0.05$) in serum triglycerides values from that of pretreatment, with percentage change +6.52%, and from that of normal group. Meanwhile, patients treated with celecoxib for 3 months showed a significant increase ($p < 0.05$) in serum triglycerides from that of pretreatment values of patients (percentage increase was +17.65%), and significantly higher values than patients treated with meloxicam for 3 months. Patients treated with meloxicam for 3 months showed no significant change ($p > 0.05$) in HDL values (percentage decrease was -3.22). As well as, patients treated with celecoxib for 3 months showed non significant increase ($p > 0.05$) in HDL values with percentage increase of +4.12%, as shown in figure- 3.

In Figure-4, Patients treated with meloxicam for 3 months showed a significant increase ($p < 0.05$) in LDL values (+12.11%) as compared to pretreatment values. Patients treated with celecoxib for 3 months showed also a significant increase ($p < 0.05$) in LDL values (+15.42%). Neither meloxicam treated patients, nor celecoxib treated patients showed a significant difference ($p > 0.05$) in serum LDL values from that of normal group.

Patients treated with meloxicam for 3 months showed an increase ($p < 0.05$) in LDL/HDL-cholesterol ratios (+14.73%) whereas, TG/HDL ratios (+10.61%, $p > 0.05$) was non significantly affected when compared to that of pretreatment values. While celecoxib showed a significant increase ($p < 0.05$) in TG/HDL ratio (+11.81%) as shown in table -2.

Treatment with either meloxicam or celecoxib produced a pronounced decrease in serum hs-C reactive protein values to variable degrees. Patients treated with celecoxib were presented with greater lowered values of C-reactive protein after 3 months period (Figure-5).

Patients treated with celecoxib for 3 months showed non significant change ($p > 0.05$) in serum creatine kinase activity from that of normal group, nor from that of pretreatment values. However, meloxicam showed a significant reduction ($p < 0.05$) in serum creatine kinase (table- 3).

Serum AST activity was increased by 72.8% in patients treated with meloxicam as well as those treated with celecoxib (percentage increase was 50%) as shown in table -4. Serum urea exhibited significant increase after treatment with both meloxicam & celicoxib (table-5). However, treatment with meloxicam showed significant increase in serum creatinine values but, celicoxib not affected creatinine concentration table-6.

Discussion

Several epidemiological studies provide indirect support; that there is an association between high resting levels of inflammatory markers, such as CRP with both the incidence of acute cardiovascular events ^[27] and the prevalence of carotid artery plaques in patients with RA ^[28].

In our study, rheumatic patients were presented with total serum cholesterol (TC) levels that are statistically non significantly different from that of normal group of subjects (figure -1). The same was true for that of HDL-cholesterol (figure -3). However, serum triglycerides values were significantly lowered. Dyslipidaemia has been well documented in RA ^[29]. During active RA, both total and LDL-cholesterol are changed (may be elevated or reduced) ^[30], but HDL-cholesterol is consistently reduced, leading to unfavorable lipid profile ^[31]. Elevated serum total cholesterol and HDL-C levels in RA are inversely correlated with disease activity, suggesting a potential role for inflammation in the atherogenic profile and the higher atherosclerotic risk observed in RA ^[32].

Since triglycerides/HDL ratio was not significantly altered after treatment with meloxicam when compared to that of pretreatment and normal groups (table-2). This may indicate that meloxicam affects lipids quantitatively but not qualitatively. i.e. enhances LDL-Cholesterol formation but not affecting the size of LDL particles which is an important atherogenic factor ^[33]. Whereas, celecoxib treatment produced a significant qualitative rather than quantitative changes presented by higher TG/HDL-C levels. When meloxicam and/or celecoxib increases serum total cholesterol levels and LDL-C and serum triglycerides from baseline values, this will lead to increase in cardiovascular risks in arthritis patients who are originally with cardiovascular risk ^[34]. This was also agreed with other studies that confirm modified lipid profile was associated with cardiovascular risk ^[35, 36]. Out of 11 atherothrombotic biomarkers assessed at baseline, the total cholesterol/HDL-C ratio and CRP were the strongest independent predictors for development of peripheral arterial disease ^[37]. Meanwhile, patients treated with celecoxib exhibited a greater reduction in serum hs-CRP values from that of pretreatment values as well as those treated with meloxicam. However, these values still higher than the control values (figure -5). This might indicate that celecoxib could exert a greater anti-inflammatory effect.

A selective inhibitor of COX-2, celecoxib, could significantly improve endothelium-dependent vasodilatation; also, C-reactive protein was significantly lowered after celecoxib treatment compared to a placebo. Both effects could be relevant to chronic inflammation ^[38]. The observed beneficial effects of celecoxib on endothelial function may in part be explained by the reduction of hs-CRP, an exquisite marker of low-grade chronic inflammation and a strong independent predictor of future cardiovascular events ^[39]. CRP-mRNA is

increased in the atherosclerotic vasculature^[40] and reflects the vulnerability of the atheromatous lesion and the likelihood of a plaque to rupture^[41]. However, a recent randomized trial of meloxicam (a relatively COX-2 selective NSAID) compared with a placebo suggested a reduction in cardiovascular outcomes^[42].

Creatine kinase enzyme activity plays a role in diagnosis of ischemic heart disease could be reduced in some conditions, including some rheumatic diseases, by unknown mechanism^[43]. Remy et al (2003) demonstrated that selective COX-2 inhibition by celecoxib reduces low-grade chronic inflammation and oxidative stress in coronary artery disease^[44], Hence, such effects could play a significant role in decreasing serum creatine kinase activity values as the enzyme is released from the myocardium after any damage that affect myocardium from coronary impairment or insufficiency.

Aspartate transaminase activity increased significantly in patients treated with either meloxicam or celecoxib such increase may be of liver origin due to drugs effect on hepatobiliary system, or may be of myocardial origin and this predicts a future risk of cardiovascular system. However, several studies indicated that Celecoxib has been associated with hepatitis and pancreatitis^[45,46].

Patients treated with celecoxib showed a significantly lowered serum creatinine values than normal and meloxicam treated patients. meloxicam could increase both serum creatinine and urea levels. The renal function could be overestimated from serum creatinine level in patients with long-standing and advanced RA because of their muscle atrophy^[47,48]. However, short-term studies of renal effects of Cox-2 inhibitors in healthy males or elderly patients demonstrated transient decreases in renal blood flow and glomerular filtration rate (GFR)^[49,50].

Moreover, Cox-2-stimulated prostaglandins attenuate glomerular arteriolar constriction associated with tubular glomerular feedback in a paracrine fashion. This protective mechanism of maintaining glomerular perfusion may be attenuated by Cox-2 inhibitors, leading to sustained glomerular arteriolar constriction, renal hypoperfusion and pre-renal azotaemia^[51, 52].

As a conclusion, the selectivity of COX-2 inhibitors is not the major character of these drugs to affect cardiovascular risk markers in patients with RA, since both purely selective (celecoxib) and relatively selective (meloxicam) inhibitors of COX-2 exhibited a comparable effects on lipids, although meloxicam could adversely affects to a greater degree some myocardial markers (CK, AST), as well as, it may deteriorate kidney function in those patients.

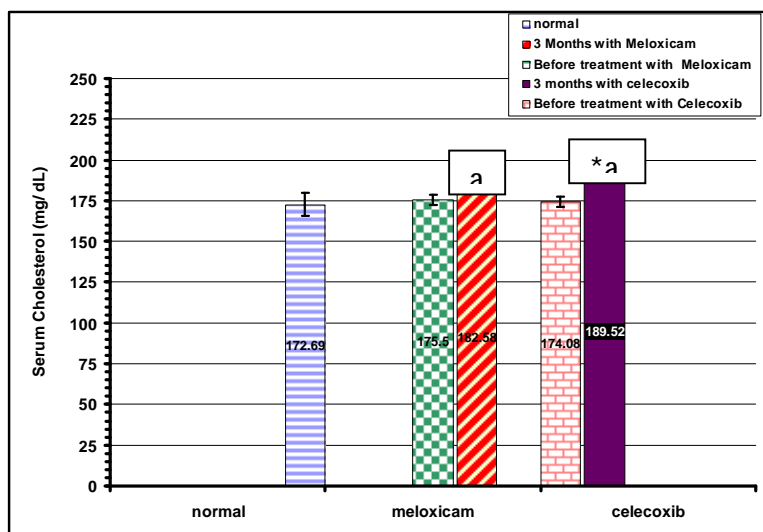


Figure 1: A histogram showing effect of treatment with celecoxib and meloxicam for three months, on total serum cholesterol (mg/dl); in patients with rheumatoid arthritis as compared with pretreatment & normal individual that not received any NSAID.

*Significantly different ($p < 0.05$) as compared with normal values.

A significantly different ($p < 0.05$) as compared with Pretreatment values.

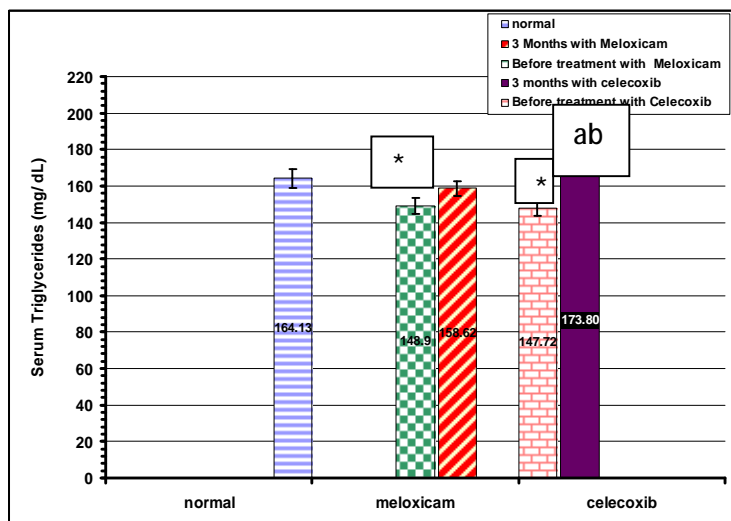


Figure 2: A histogram showing effect of treatment with celecoxib and meloxicam for three months, on Serum triglycerides (mg/dl); in patients with rheumatoid arthritis as compared with pretreatment & normal individual that not received any NSAID.

* Significantly different ($p < 0.05$) as compared with normal values.

a=significantly different ($p < 0.05$) as compared with Pretreatment values.

b= significantly different ($p < 0.05$) as compare Celecoxib with meloxicam groups.

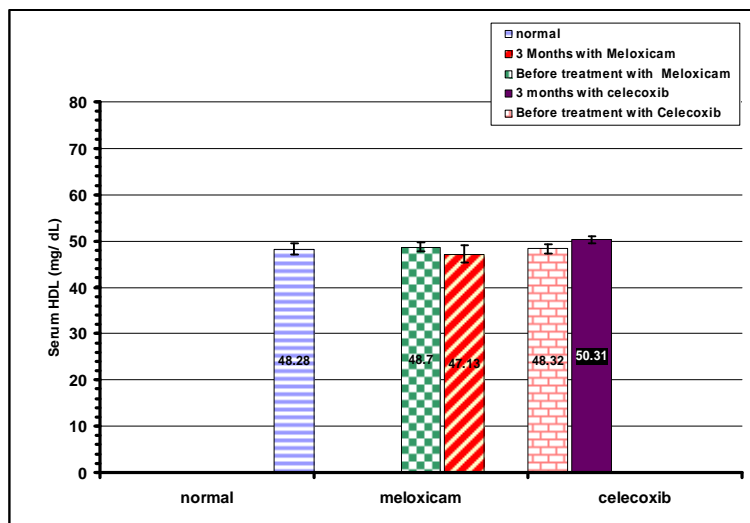


Figure 3: A histogram showing effect of treatment with celecoxib and meloxicam for three months, on plasma concentrations of HDL in mg/dl, in patients with rheumatoid arthritis as compared with pretreatment & normal individual that not received any NSAID.

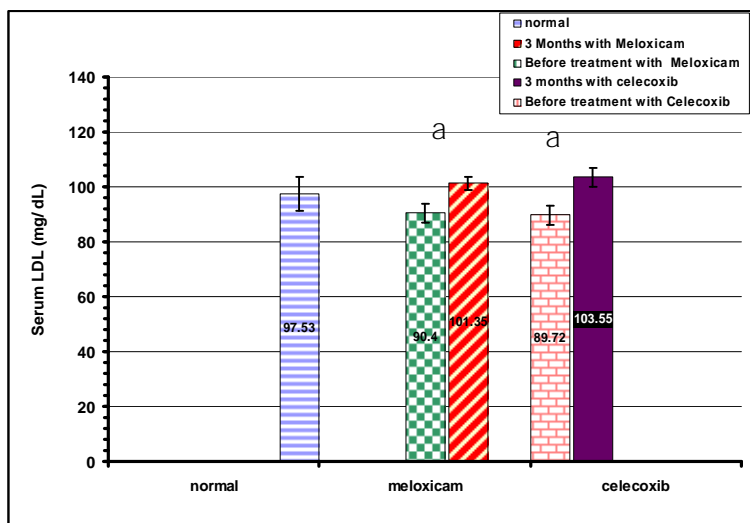


Figure 4: A histogram showing effect of treatment with celecoxib and meloxicam for three months, on plasma concentration of LDL in mg/dl; in patients with rheumatoid arthritis as compared with pretreatment & normal individual group that not received any NSAID.

a = significantly different (p<0.05) as compared with Pretreatment values.

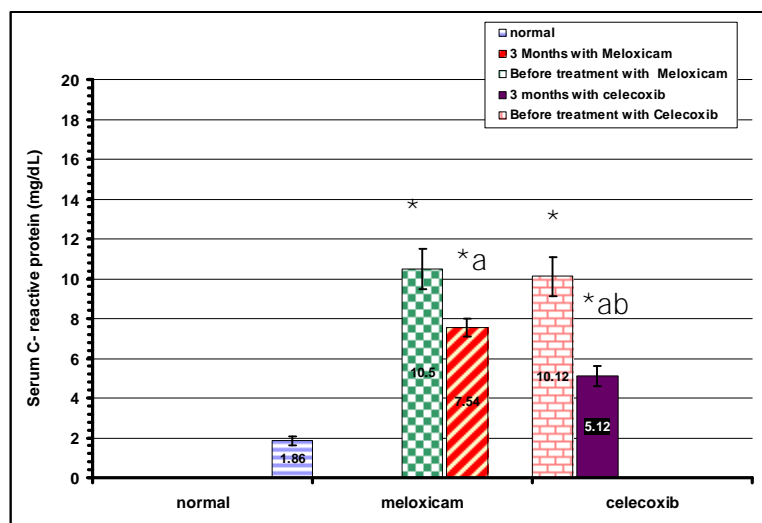


Figure 5: A histogram showing effect of treatment with celecoxib and meloxicam for three months, on serum C-reactive Protein (mg/dl), in patients with rheumatoid arthritis as compared with pretreatment & normal individual groups that not received any NSAID.

Values expressed as mean \pm standard error of mean.

* Significantly different ($p < 0.05$) as compared with normal values.

a=significantly different ($p < 0.05$) as compared with pretreatment values.

b=significantly different ($p < 0.05$) as compare celecoxib with meloxicam groups.

Groups	Number of subjects	LDL/HDL ratio		Δ %Change
		pretreatment	After 3 months treatment	
Normal	12	2.04 \pm 0.14		
Meloxicam	12	1.90 \pm 0.08	2.18 \pm 0.09 a	+ 14.73
Celecoxib	24	1.87 \pm 0.08	2.068 \pm 0.074	+ 10.54

Table 1: Effect of celecoxib and meloxicam treatment on LDL/HDL-cholesterol ratio, in patients with rheumatoid arthritis; as compared to pretreatment values and to the normal individuals (that not received any NSAID). Values expressed as mean \pm standard error of the mean.

Values expressed as mean \pm standard error of mean.

a = significantly different ($p < 0.05$) as compared with pretreatment values.

Groups	Number of subjects	Triglycerides/HDL ratio		Δ %Change
		pretreatment	After 3 months treatment	
Normal	12	3.42 ± 0.13		
Meloxicam	12	3.1 ± 0.12	3.42 ± 0.15	+ 10.32
Celecoxib	24	3.09 ± 0.12	3.46 ± 0.06 a	+ 11.81

Δ =Percentage change was calculated as compared to pretreatment values.

Table 2: Effect of celecoxib and meloxicam treatment on Triglycerides/HDL ratio, in patients with rheumatoid arthritis; as compared to pretreatment values and to the normal individuals (that not received any NSAID). Values expressed as mean ± standard error of the mean.

Values expressed as mean ± standard error of mean.

a significantly different (p<0.05) as compared with pretreatment values.

Δ Percentage change was calculated as compared to pretreatment values.

Groups	Number of subjects	Serum creatine kinase (IU/Liter)		Δ %Change
		pretreatment	After 3 months treatment	
Normal	12	51.17 ± 7.29		
Meloxicam	12	49.4 ± 2.70	59.33 ± 6.25	+ 20.10
Celecoxib	24	49.04 ± 2.64	45.63 ± 2.42 b	- 6.97

Table 3: Effect of celecoxib and meloxicam treatment on serum creatine kinase (IU/liter) Aspartate in patients with rheumatoid arthritis; as compared to pretreatment values and to the normal individuals (that not received any NSAID). Values expressed as mean± standard error of the mean.

Values expressed as mean ± standard error of mean.

b = significantly different (p<0.05) as compare Celecoxib with meloxicam groups.

Δ = Percentage change was calculated as compared to pretreatment values.

Groups	Number of subjects	Serum AST(IU/Liter)		Δ %Change
		pretreatment	After 3 months treatment	
Normal	12	8.19 ± 1.52		
Meloxicam	12	6.8 ± 0.91	11.75 ± 1.36 a	+ 72.8
Celecoxib	24	6.71 ± 0.89	10.06 ± 0.80 a	+ 50

Table 4: Effect of celecoxib and meloxicam treatment on serum AST (IU/liter), in patients suffered from rheumatoid arthritis; as compared to pretreatment values and to the normal individuals (that not received any NSAID). Values expressed as mean ± standard error of the mean.

Values expressed as mean ± standard error of mean.

a significantly different (p<0.05) as compared with pretreatment values.

Δ Percentage change was calculated as compared to pretreatment values.

Groups	Number of subjects	Serum urea (mg/dl)		Δ %Change
		pretreatment	After 3 months treatment	
Normal	12	24.56 ± 1.15		
Meloxicam	12	25.1 ± 0.96	28.96 ± 1.77 *	+ 15.37
Celecoxib	24	24.91 ± 0.94	29.33 ± 0.85 *a	+ 17.75

Table 5: Effect of celecoxib and meloxicam treatment on serum urea (mg/dl) in patients with rheumatoid arthritis; as compared to pretreatment values and to the normal individuals (that not received any NSAID). Values expressed as mean ± standard error of the mean.

Values expressed as mean ± standard error of mean.

*Significantly different (p<0.05) as compared with normal values.

a significantly different (p<0.05) as compared with pretreatment values.

Δ Percentage change was calculated as compared to pretreatment values.

Groups	Number of subjects	Serum Creatinine (mg/dl)		Δ %Change
		pretreatment	After 3 months treatment	
Normal	12	0.96 ± 0.07		
Meloxicam	12	0.8 ± 0.03 *	0.96 ± 0.07 a	+ 20
Celecoxib	24	0.79 ± 0.03 *	0.77 ± 0.03 *b	- 2.27

Table 6: Effect of celecoxib and meloxicam treatment on serum creatinine (mg/dl), in patients with rheumatoid arthritis; as compared to pretreatment values and to the normal individuals (that not received any NSAID). Values expressed as mean ± standard error of the mean.

Values expressed as mean ± standard error of mean.

*Significantly different (p<0.05) as compared with normal values.

a significantly different (p<0.05) as compared with pretreatment values.

b significantly different (p<0.05) as compare celecoxib with meloxicam groups.

Δ Percentage change was calculated as compared to pretreatment values.

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