

Safety of Celecoxib versus standard non steroidal anti inflammatory drugs with respect to renal function in type 2 diabetes

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Abstract

The most common therapy utilized to control musculoskeletal system pain in diabetics are nonsteroidal anti inflammatory drugs (NSAIDs) which permit their action by inhibiting cyclooxygenase enzyme (COX). **The aim of study:** To study the effect of relatively selective Cox2 inhibitor (diclofenac) and highly selective Cox2 inhibitor (celecoxib) on renal function in hyper and normolipidemic type 2 diabetics. **Patients and method:** Thirty-four subjects were involved in this study, (11 males, 23 females) of them are type 2 diabetes having musculoskeletal pain (with an age range of 40-55) and a Control group of 16 (male=7, female=9) apparently healthy subjects (with an age range of 40-57 years). The diabetic patients were classified according to their serum lipid profile into 2 groups: The first group Included 20 hyperlipidemic diabetic patients (total cholesterol ≥ 5.18 mmol and/or triglyceride ≥ 1.69 mmol/l) with musculoskeletal pain, (13) of them were treated with celecoxib 200mg for 8 weeks, while the remainders, (7) were treated with diclofenac 100mg/day for 8weeks. The second group included 14 normolipidemic diabetic patients with musculoskeletal pain, (7) of them treated with celecoxib 200mg /day for 8 weeks. The third group included 16 (male=7, female=9) apparently healthy subjects (with an age range of 40-57 years) as Control group. Fasting plasma glucose (FPG), Lipid profile, renal function parameters (serum urea and creatinine) were evaluated at baseline and after receiving either celecoxib or diclofenac therapy. **Results:** Diclofenac produce a significant increase in serum urea and creatinine concentration in both hyper and normolipidemic diabetics, whereas, celecoxib produce a significant elevation in serum urea concentration without a significant alteration in serum creatinine concentration. **Conclusion:** Administration of highly selective COX2 inhibitor (Diclofenac) to normolipidemic and hyperlipidemic type 2 diabetics is better than relatively selective COX2 inhibitor (celecoxib) in concern to renal function.

Key words: Cyclo-oxygenase 2 inhibitors, creatinine, type2 diabetes, urea

INTRODUCTION

Dyslipidemia associated with type 2 diabetes mellitus (DM) is typically more complex than simple elevation of systemic low-density lipoprotein cholesterol (LDL-C) levels. In fact, the LDL-C levels seen in diabetic populations may not be significantly different from the values seen in non diabetic populations [1]. The high atherogenicity associated with diabetic dyslipidemia is probably related to the characteristic finding of low plasma concentrations of HDL-C, elevated levels of apolipoprotein B and elevated TG levels, as well as to abnormalities in lipoprotein particle size and subclass distribution [2]. Several mechanisms may account for atherogenic lipid abnormalities in diabetic patients. Dysfunctional adipose tissue or adiposopathy is thought to develop via the combination of excessive fat accumulation and genetic predisposition. There is also evidence suggesting an association between diabetes and cyclooxygenase-2-mediated inflammation [3]. Cyclooxygenase has been demonstrated to exist as two main isoforms, COX-1 is constitutively expressed in nearly all tissues. Cox-2 expressed by cells that are involved in inflammation (e.g., macrophages, monocytes, synoviocytes). Cox-3 has been recently proposed may exist in

the brain. Non-steroidal anti inflammatory drugs named NSAIDs, because they are structurally different from steroidal anti inflammatory drugs [4]. As NSAIDs possess analgesic, antipyretic and anti inflammatory effects [5]. Mechanism of action by inhibition of COX activity. [6- 8]. Celecoxib, rofecoxib, and valdecoxib, however these drugs may have therapeutic action similar to these of non-specific COX-2 inhibitors, but without causing the unwanted side effects [9]. NSAID classified to:

1. Selective cox1 inhibitor ex. aspirin
2. Non selective cox-1 inhibitors ex. ibuprofen, naproxen, indomethacin
3. Relatively selective cox-2 inhibitors ex. diclofenac
4. Highly selective cox-2 inhibitors ex. celecoxib, rofecoxib

Celecoxib is a non steroidal anti inflammatory drugs (NSAIDs), acts as a selective inhibitor of cyclooxygenase-2 (COX-2) [9]. As with other NSAIDs selective cox-2 inhibitors it should be avoided in patients with chronic renal insufficiency. The metabolites are excreted in urine and feces. Patients with chronic renal insufficiency appear to have 435 lower plasma concentrations compared to healthy individuals [10]. Diclofenac is a non steroidal anti inflammatory drugs a relatively selective inhibitor

of cox-2 [11]. and metabolized in the liver and excreted in urine 65% and bile 35 % [12].

PATIENT AND METHODS

This study was carried out at the national diabetes center, Al Mustansiriyah University. The study included 34 patients with type 2 diabetics having musculoskeletal pain on oral anti diabetic drugs. Patients with (pregnancy ,breast feeding ,hypertensive ,Ischemic heart disease ,peptic ulcer, on hypolipidemic drugs, allergic to sulfa drugs) were excluded. Selected patients were categorized into 3 groups; **First group:** included 20 hyperlipidemic (total serum cholesterol ≥ 5.18 mmol/l and or TG ≥ 1.69 mmol/l) diabetic patients (7males and 13 females) with musculoskeletal pain. (13) Of them were treated with celecoxib 200mg/day taken as single dose for 8 weeks, while the remainder (7) was treated with diclofenac 100mg/day for 8 weeks. **Second group:** included 14 normolipidemic diabetic patients (4males and 10 females) with musculoskeletal pain. (7) Of them treated with celecoxib 200mg/day and (7) treated with diclofenac 100mg/day for 8 weeks. **Third group** included 16 apparently healthy subjects (7males and 9 females) considered as control group. Fasting blood glucose, urea, creatinine, lipid profile were evaluated.

STATISTICAL ANALYSIS

1. The results were expressed as mean \pm standard error of mean.
2. Student t-test and analysis of variance (ANOVA) were used to examine the degree of significant. P-value less than 0.05 considered significant.
3. The statistical analysis was performed using Microsoft excel program 2003.

Results: The table showed that treatment of hyperlipidemic diabetics with diclofenac for 8 weeks resulted in a significant increase ($p < 0.05$) in both blood urea and creatinine concentrations as compared to the base line values (% changes were +26.51, +9.54).meanwhile treatment with celecoxib resulted in a significant elevation ($p < 0.05$) in blood urea concentration (5 changes+18.61) with a non significant changes in serum creatinine concentration (%changes+3.98) as compared with the base-line values.

Table 1: The comparison of antropometric and biochemical parameters among study groups

Group	Type of therapy	Duration of therapy	Serum urea (mmol/l)	Serum creatinine (mmol/l)
Control N=16			4.42 \pm 0.15	53.86 \pm 4.33
Hyperlipidemic N=20	Diclofenac N=7	Baseline after 8weeks	5.50 \pm 0.48*a 6.95 \pm 0.73*b 4.53 \pm 0.25a	65.53 \pm 7.94 a 71.79 \pm 7.79*b 74.58 \pm 6.98*a
	Celecoxib N=13	Baseline after 8 weeks	5.37 \pm 0.33*b	77.55 \pm 6.49*a

Normolipidemic N=14	Diclofenac N=7	Baseline After 8 weeks	4.62 \pm 0.51 a 5.74 \pm 0.80 b 4.43 \pm 0.31 a	66.85 \pm 9.91 a 73.65 \pm 12.50 b
	Celecoxib N=7	Baseline After 8 weeks	5.02 \pm 0.33 b	69.18 \pm 9.38 a 65.60 \pm 8.92 a

* $p < 0.05$ with respect to control group Non identical superscript (a,b) within the same drug treated group represent significant difference , $p < 0.05$.

Discussion

This study showed that baseline levels of blood urea and creatinine concentrations in hyperlipidemic patients were significantly higher than that of controls indicating that hyperlipidemic diabetics might have a reduction in their renal function. Several studies showed that hyperlipidemia exerts a deleterious affection the kidneys[13,14] the possible mechanism linking hyperlipidemia with deterioration of renal function is through lipid deposition in the glomerulus and renal tubule-interstitial cells leading to increase in glomerular matrix and cellularity, glomerular and tubule -interstitial macrophage influx and increased tubular epithelial cell turn over. All these factors can lead to decline in renal function[14].although, their blood urea and creatinine concentrations were elevated in these groups of patients, but their levels were within the refer limit. In this study, both highly selective cox-2 inhibitor (celecoxib) and relatively selective cox-2 inhibitor (diclofenac) have been associated adverse effects on renal function. Clinical studies showed that both COX-1 and COX-2 are expressed in the kidney and contribute to the regulation of renal function. COX-1 is detected in the collecting duct, in the loop of henle, portions of renal vasculature and was believed to have role in renal hemodynamic regulation through generation of PGI2 [9]. Meanwhile COX-2 immune-reactivity was observed in the renal vasculature, medullary interstitial cells and muscular densa. In the renal cortex, COX-2 expression increases in high rennin states, and selective COX-2 inhibitors significantly decrease plasma rennin levels. In the medullary region of the kidney, the expression of COX-2 increase in response to high salt diet and water deprivation (15).COX-2 catalysis the production of both PGI1 and PGI2 in the kidney. Since, PGE2 diminishes sodium reabsorption, thereby, its inhibition results in sodium retention that can be clinically in a variety of ways, such as peripheral edema, weight gain, and increased blood pressure. While PGI2 increases potassium secretion, preserves renal blood flow and glomerular filtration rate, so its inhibition may lead to hyperkalemia (particularly in patients with underlying renal insufficiency) and acute renal failure (in conditions of decreased actual or effective circulating volume [15, 16]. The study showed that the diclofenac treatment in diabetic patients produced a greater effect on renal function than celecoxib treatment, as manifest by a significant increase in serum creatinine concentration. Several clinical studies showed that renal effect of selective COX-2 inhibitors are similar to those of other NSAIDs, and both selective COX-2 inhibitors and NSAIDs may cause peripheral edema, hypertension and exacerbation of pre existing hypertension by inhibiting water and salt excretion by the kidney (15,17,18).Although,

decreased sodium excretion was comparable between NSAIDs and specific COX-2 inhibitors, only NSAIDs were able to reduce the glomerular rate in volunteers with normal renal function [15,18]. A recent randomized controlled trial compared standard dosing of diclofenac (75mg twice daily) and ibuprofen (800mg 3 times daily) with high dose celecoxib (400mg twice daily) for patients with normal kidney function being treated for osteoarthritis and rheumatoid arthritis. The mean increase in serum creatinine in the celecoxib group was less than that noted in the diclofenac controls with no difference in mean serum creatinine was detected among those patients using ibuprofen (800mg 3 times daily) compared with those using high dose celecoxib. Such evidence could further support the safety of celecoxib versus standard NSAIDs with respect to renal dysfunction [19, 20].

Conclusion: Administration of highly selective COX2 inhibitor (Diclofenac) to normolipidemic and hyperlipidemic type 2 diabetics is better than relatively selective COX2 inhibitor (celecoxib) in concern to renal function..

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