Effects of non-steroidal antiinflammatory drugs on the glycemic satae and inflammatory marker in poorly controlled type ii dm patients

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الخلاصة

أثبتت دراسات متعددة العلاقة بين ارتفاع مستوى المعايير الالتهابية مثل CRP واحتمالية الإصابة بداء السكري في المستقبل ومضاعفاته ، لكن العلاقة بين هذه الظاهرة ودور الإنزيم COX المفترض مازالت غير واضحة بشكل تام . ومن خلال هذه الدراسة نحاول تقديم أدلة قائمة على نتائج سريرية حول إمكانية الاستخدام السريري لمثبطات الإنزيم COX-2 الانتقائية والشاملة في السيطرة على مستوى الكلوكوز لدى مرضى داء السكري الذين فشلت العقاقير الخافضة للكلوكوز في تحقيقها .

أجريت الدراسة على (38) مريضا بداء السكري من النوع الثاني (12 ذكر ا و26 أنثى) و بمعدل عمر(55) سنة والخاضعين للعلاج لمدة معدلها (6,5) سنة و لكن بدون استجابة تامة ، وتم تقسيمهم إلى ثلاثة مجاميع ، المجموعة الأولى تم علاجها بعقار روفيكوكسب 25 ملغم\يوم والمجموعة الثانية بعقار دايكلوفيناك 100 ملغم \ يوم ولمد شهرين ، أما المجموعة الثالثة فقد استخدمت كمجموعة سيطرة وبدون علاج من هذا النوع .

تم قياس مستويات FSG و HbA1c , S.Creatinin , CRP, BMI قبل البدء بالعلاج وبعد شهرين من الاستمرار عليه .

أظهرت الدراسة عدم قدرة التداخل العلاجي باستخدام العقاقير المضادة للالتهابات غير الستيرويدية (روفيكوكسب و دايكلوفيناك) وللفترة الزمنية المذكورة من تحقيق نتائج ذات فرق معنوي في السيطرة على مستوى الكلوكوز على الرغم من خفض نسبة معيار الالتهاب CRP.

من خلال النتائج التي تم الحصول عليها يمكن الاستنتاج بان دور الإنزيم COX في العملية الالتهابية المصاحبة لداء السكري قد لا يكون هو العامل الأساسي بهذا الشأن ، وان الأمر بحاجة إلى دراسات سريرية أخرى أكثر شمولا لتسليط المزيد من الضوء على هذا الموضوع .

ABSTRACT

Recent studies have shown that inflammatory markers like C-reactive protein (CRP) predicts future risk of diabetes mellitus (DM), and the data about the relationship between inflammation and the role of cyclooxygenase (COX) enzyme with type 2 DM are scar. In the present study, the clinical use of COX-inhibitors to improve glycemic state in type 2, poorly controlled DM patients was tested. Thirty eight(38) type 2 diabetic patients (12 males and 26 females) with age range of 55±S.E.1.25yrs., who are maintained on hypoglycemic agents for 6.5±S.E.0.92 years, but with poor glycemic control, were included in the study and randomly allocated into 3 groups; first group was treated with 25mg/day rofecoxib and the second was treated with 100 mg/day diclofenac for 2 months. The third group served as control for comparison. Fasting serum glucose (FSG), glycated hemoglobin (HbA1c), CRP and body mass index (BMI) were evaluated pre- and post-treatment. All the poorly controlled type 2DM patients included in the study were presented with high CRP levels. Treatment with rofecoxib and diclofenac for 60 days, showed relatively non-significant decrease in CRP, and did not produce any significant improvement in glycemic control. It could be concluded that COX pathway may not be the major contributor to the inflammatory events associated with DM and its associated complications. Further extensive pharmacologically based evaluation in this respect was necessary.

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INTRODUCTION :

An accumulating body of evidence suggests that inflammation may play a crucial intermediary role in the pathogenesis of diabetes mellitus (DM), thereby linking diabetes with a number of commonly coexisting conditions thought to originate through inflammatory mechanisms[1]. Several cross-sectional studies showed that type 2DM but not type 1DM were commonly associated with elevated levels of inflammatory markers (acute–phase proteins and pro-inflammatory cytokines) in comparison with nondiabetic subjects after matching for age, sex, glycemic control and absence of tissue complications[2]. Serum levels of acute-phase proteins and pro-inflammatory cytokines showed a graded increase with increasing features of metabolic syndrome in type 2DM and nondiabetic subjects (e.g. obesity, coronary heart disease and dyslipidemia)[3]. Experimental studies using different drugs with anti-inflammatory action reducing inflammatory markers (e.g. CRP) in parallel with reducing risk of developing type 2DM and improving control in established diabetes[4,5].

Because PGE2 is an inhibitor of glucose–induced insulin secretion, it follows that a high basal activity of COX−2 might serve to modulate insulin release leading to glucose intolerance and play a role in the pathogenesis of type 2 diabetes[6].

The relationship between various patterns of inflammatory events, and associated complications of diabetes mellitus were extensively studied both *in vivo* and *in vitro*; and large number of observations in this respect also published concerning the biochemical, epidemiological and pathophysiological aspects of this issue[7–15]. However, no enough pharmacologically based evidences were available to enable utilizing this approach as an effective way for the management of DM and its complications. So, this study was designed to provide pharmacologically based clinical data which confirm the already available one about the relationship between the inflammatory process and glycemic control; and to Evaluate the possibility of pharmacological intervention through the use of selective and non selective COX-2 inhibitors, to support the glycemic control, which is already poorly attained by the ordinary oral hypoglycemic agents.

PATIENTS AND METHODS:

This study was carried out on type 2 diabetic patients with poor glycemic control at the Specialized Center for Diabetes and Endocrinology, Al-Kindi Teaching Hospital, Baghdad, according to the following criteria for patient selection:

1. Patients should have type 2DM, maintained on oral hypoglycemic agents, and not receiving insulin therapy.
2. Pregnants and breast – feeding mothers were not included.
3. Patients who have diabetic foot, other infections or diagnosed chronic inflammatory disease were excluded.
4. Patients with a history of gastrointestinal tract problem, peptic and duodenal ulcers were excluded.

Total number of diabetic patients selected were (107) with age range of (53±1.72 years) and duration of the disease were (6.5±0.92) years, males constitute (41, 38.32%) and females (66, 61.68%). Of the (107) diabetic patients included in this study, (50, 46.73%) patients (10 males and 40 females) have positive reaction for C–reactive protein (CRP≥6 mg/l) measured by simple agglutination test, while (57, 53.27%) patients (31 males and 26 females) have negative reaction for CRP. Of the former (50) participants who have positive CRP reaction, only (38) patients completed the study and (12) patients were excluded. Those (38) diabetic patients (12 males and 26 females) with mean age of (55 ± 1.25) years and mean duration of the disease of (6.2 ± 0.75) years were randomly allocated into three groups and treated as follow:

1. Group A: 17 patients (8 males and 9 females), treated with rofecoxib tablets 25mg/day taken at morning after meals for 2 months in addition to the routinely used oral hypoglycemic agent.
2. Group B: 12 patients (2 males and 10 females), treated with diclofenac tablets 50mg twice daily taken at morning and evening after meals for 2 months in addition to the routinely used oral hypoglycemic agent.
3. Group C: 9 patients (3 males and 6 females) kept on their routinely used oral hypoglycemic agent without any anti-inflammatory agent of any type, served as controls.
Fasting serum glucose (FSG)[16], glycosylated hemoglobin (HbA1c)[17], C-reactive protein (hs-CRP)[18] and body mass index (BMI)[4] are measured according to standard methods before starting the treatment (as zero time level) and after 2 months of treatment .
The results were expressed as mean ± standard error. The results analyzed statistically utilizing paired t-test for the pre- and post- treatment values in each group. ANOVA and Bonferroni tests were used to compare intergroup variation. Values with $P<0.05$ considered significantly different .

RESULTS:

Effects of treatment on glycemic state in DM patients

The data presented in table (1) showed that FSG level was not significantly affected due to treatment with rofecoxib for 2 months. In this group the level of glycated hemoglobin (HbA1c) remain unchanged, where no significant differences were observed after 60 days of treatment compared to pre-treatment levels. Table (1) also demonstrated that the already elevated FSG levels in group (B) were significantly reduced (25 %, $P< 0.05$) compared to pre-treatment levels; but treatment with 100mg/day diclofenac for 2 months didn't change the level of protein glycation (HbA1c) significantly. Meanwhile, no significant changes in the glycemic control parameters were observed in the DM patients who didn't receive any type of NSAIDs used in the study and followed at comparable conditions. Statistical analysis of significance didn't reveal any differences among different groups of patients included in the study concerning glycemic control.

Table 1 . Effects of treatment with 25mg/day rofecoxib and 100mg/day diclofenac on FSG and HbAlc levels in DM patients.

Patient Groups	Fasting Serum Glucose mmol/l		HbAlc %	
	Pre-treatment	After 2 months	Pre-treatment	After 2 months
Group A n = 17	9.035 ± 0.868	9.094 ± 0.91	6.147 ± 0.55	6.2 ± 0.512
Group B n = 12	12.275 ± 1.46	9.2* ± 1.031	7.941 ± 0.75	8.025 ± 0.697
Group C n = 9	8.8 ± 0.87	11.4 ± 1.745	8.011 ± 1.021	8.0 ± 0.894

Values represent mean ± standard error.
n = number of subjects.
(*) Significantly different ($P<0.05$) with respect to pre-treatment in each group.

Effects of treatment on CRP levels in DM patients

In table (2), treatment of DM patients (group A) with selective COX-2 inhibitor rofecoxib (25mg/day) for 2 months resulted in 40% decrease in CRP levels which are already elevated in those patients, but even with such a decrease obtained, no significant differences ($P >0.05$) were observed compared to pre-treatment levels.

Concerning the use of non-selective COX-2 inhibitor diclofenac (100mg/day), it also produces 46% decrease in CRP levels in group B patients compared to pre-treatment values; however, even with such a level of changes, no significant difference (P>0.05) were observed in this respect (table 2). Meanwhile, group C which includes DM patients with poor glycemic control and not received any type of NSAIDs demonstrated 38% increase in CRP levels in their serum, but still it is non-significant with respect to pre-treatment values (table 2). Statistical analysis utilizing ANOVA and Bonferroni tests were used and the result was non–significant difference among the groups.

Table 2 . Effects of treatment with 25mg/day rofecoxib and 100mg/day diclofenac on CRP levels and BMI in DM patients.

Patient Groups	Serum CRP mg/l		BMI (kg/m^2)	
	Pre-treatment	After 2 months	Pre-treatment	After 2 months
Group A n = 17	10.599 ± 3.839	6.365 ± 2.663	27.782 ± 0.573	28.4** ± 0.552
Group B n = 12	13.613 ± 3.512	7.345 ± 1.953	29.4 ± 2.317	30.141* ± 2.408
Group C n = 9	7.262 ± 2.231	10.023 ± 2.002	29.877 ± 1.682	30.433* ± 1.643

Values represent mean ± standard error.
n = number of subjects.
(*) Significantly different (P<0.05) with respect to pre-treatment in each group.
(**) Highly significant difference (P<0.01) with respect to pre-treatment in each group.

Effects of treatment on the body mass index (BMI) in DM patients

Table (2) demonstrated that treatment of DM patients with 25mg/day rofecoxib (group A) resulted in highly significant increase (P<0.01) in BMI, while its value after 2 months in groups B and C was significantly (P<0.05) elevated compared to baseline values. No significant differences were observed in this respect among all patient groups when the data analyzed by ANOVA or Bonferroni tests (table 2).

DISCUSSION:

The Effect of Treatment with NSAIDs on the Glycemic State

In the present study, both selective and non-selective COX-2 inhibitors (rofecoxib and diclofenac) didn't show significantly different effects on glycemic control, however, diclofenac shows significant improvement in FSG level, this could be explained by the fact that islet amyloid polypeptide (IAPP, amylin) which is synthesized by the B-cells and co-secreted with insulin, favors polymerization into insoluble amyloid fibrils[19-21]; and the deposition of these beta-sheet polypeptide fibrils as amyloid deposits is considered to play a central role in the pathophsiology of type 2DM. These deposits were found at post partum in up to 96% of type 2 diabetics[22,23]. Those amyloid deposits, comprises of beta-sheet fibrillar amylin compromise islet function and result in B-cells destruction with consequent inhibition of insulin secretion[24,25]. Recently, it was found that NSAIDs prevented and reversed the beta–sheet conformation of human amylin with expected amelioration of the disease process in type 2DM. Selective COX-2 inhibitors were found less effective in this respect[26], an observation which is quite compatible with the finding of this study.

All DM patients included in this study were overweight (BMI>27); and body fat was found to play an important role in DM, where diabetic patients have increased rates of lipolysis and raised levels of non-esterified free fatty acids (NEFA), which may contribute to worsen hyperglycemic state through the stimulation of hepatic gluconeogenesis[27,28], and inhibition of glucose utilization by skeletal muscles due to a decrease in the glucose oxidase activity[29]. So, combination of increased hepatic glucose output from the liver and reduced peripheral uptake effectively antagonizes the action of insulin and ultimately lead to hyperglycemia even when COX−2 inhibition by rofecoxib increases insulin release. Accordingly, further studies to measure the extent of insulin release in this situation become of interested concern.

Effects of Treatment with NSAIDs on the Inflammatory Marker CRP

CRP is the prototype of the acute–phase proteins which shows elevated serum levels during general, non−specific response to a wide variety of stimuli. Although elevated CRP levels is not specific for any particular disease, it is a useful indicator of inflammatory process[30]. There was an accumulating body of evidence which indicate that type 2DM was associated with sustained elevation in serum CRP levels representing a state of chronic subclinical inflammation[3,31-33]; a situation where the results of this study are quite compatible with.

The results presented in table (2) clearly showed that treatment with NSAIDs produced changes in CRP levels, but statistical analysis didn't show accepted level of significance, both during pre– and post– treatment comparison, and when the data of different groups were compared. This may be related to inadequate sample of patients included in this study, and these results could provide an evidence that the elevated CRP levels in type 2DM patients might be not mediated through the COX pathway, or the COX pathway was not the major or the only triggering agent in this inflammatory event. However, because some prostaglandins (PGE2, and PGI2) might reduce the generation of toxic reactive oxygen species (ROS) in certain types of tissues or organs[34], NSAIDs could actually exacerbate tissue damage through the increase in production of toxic oxygen radicals[34].

According to the results obtained, the study confirm the association between type 2DM and elevated levels of inflammatory marker CRP suggesting chronic inflammatory process, and there is no clinical beneficial effect of using selective or non-selective COX-2 inhibitors in suppressing this inflammatory process for improving glycemic state .

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