The effect of diclofenac sodium given alone or in combination with paracetamol in treatment of patients with type-2 diabetes mellitus

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ABSTRACT

***Background*: Type-2 diabetes mellitus (T2DM), is becoming an important health problem worldwide. Diabetes mellitus may be associated with low grade chronic inflammation and oxidative stress; both of them could contribute to its pathogenesis. The use of anti-inflammatory and/or antioxidant drugs, therefore, represents a promising attempt for treatment and/or prevention of this disease.**

***Objectives*: To compare the effect of diclofenac sodium alone and when combined with paracetamol in type-2 diabetic patients not achieving target HbA1c.**

***Patients and Methods*: Twenty four, type-2 diabetic patients consulting the Center for Diabetes and Endocrinology in Maysan, south of Iraq, had managed to complete the 3 month period of the first part of this study after meeting a set of inclusion criteria. Their HbA1c was more than 7% despite the continuous use of oral antihyperglycemic drugs. The effect of diclofenac was compared with another group (n=21) that received paracetamol in addition to diclofenac sodium. Blood samples were taken from before, one month and three months after the start of treatments for measurement of HbA1c, C-reactive protein, C-peptide level and more frequently plasma glucose level (fasting/random). Another sixty patients of similar inclusion criteria were also followed for three months but without treatment and served as a control group.**

***Results*: The effect of one month treatment with diclofenac sodium alone or in combination with paracetamol resulted respectively in a reduction in HbA1c by 9.4% and 11.4%, a reduction in CRP by 62.1% and 79.6%, an increase in C-peptide by 262.5% and 216%, a reduction in FPG by 11.2% and 18.1% and a reduction in RPG by 40.3% and 24.8% in comparison to pre-treatment levels.**

The HOMA- ß C-peptide measured in a limited number of patients treated with diclofenac sodium or its combination with paracetamol showed an increase by 405.3% and 330.6% three months after start of treatment for the two groups respectively. The control, non- intervention group did not show significant changes in the levels of HbA1c over the three-month period.

***Conclusion*: Diclofenac sodium 100mg SR capsule administered once daily for one month seems to be effective in achieving a good glycemic control in patients not achieving target HbA1c. The addition of paracetamol to diclofenac did not show a clear synergistic effect, despite paracetamol beneficial effect that had been shown in a previous study.**

Key word: diclofenac sodium, paracetamol, type-2 diabetes mellitus

تأثير الدايكلوفيناك صوديوم عند اعطائه بمفرده أو مع الباراسيتامول في معالجة مرضى السكري من النوع الثاني

***خلفية الدراسة*: أصبح داء السكري من النوع الثاني مشكلة صحية مهمة على مستوى العالم، وقد يكون هذا المرض مصحوبا" بالتهابات مزمنة واطئة الشدة وأيضا" بإجهاد الاكسدة واللذان يمكن ان يسهما في مراضة السكري، فاستعمال الادوية المضادة للالتهاب لوحدها أو مع مضادات الأكسدة يمثل محاولة واعدة لمعالجة المرض أوالوقاية منه.**

***الهدف من الدراسة*: لمقارنة تاثير الدايكلوفيناك صوديوم اذا استخدم بمفرده أو مع الباراسيتامول عند مرضى السكري من النوع الثاني غير المسيطر عليه.**

***المرضى و طرائق العمل*: شملت الدراسة 24 مريضا" بالسكري من النوع الثاني والذين راجعوا مركز السكري والغدد الصماء في محافظة ميسان بعد استيفائهم لمجموعة من معايير ألاشتمال وكان الهيموغلوبين التراكمي لديهم اكثر من 7% على الرغم من الاستعمال المستمر للأدوية المنقصة للسكر العالي التي تؤخذ عن طريق الفم فكانوا هم مجموعة الدراسة. وقد تمت مقارنة تأثير الدايكلوفيناك مع مجموعة اخرى من المرضى (21 مريضا) وكانت هذه المجموعة أخذت الدايكلوفيناك بالاضافة الى الباراسيتامول. وأخذت عينات من الدم لاجراء فحوصات الهيموغلوبين التراكمي و البروتين التفاعلي نوع سي و سي بيبتايد ومستوى السكر في الدم اما عند الصوم او بشكل عشوائي لكل مريض قبل وبعد شهر وثلاثة أشهر من بدء العلاج . كما تمت متابعة ستين مريضاً اخر لمدة ثلاثة اشهر تنطبق عليهم معايير الاشتمال ولكن بدون المعالجة بالباراسيتامول واتخذت كمجموعة ضابطة.**

***النتائج*: ان المعالجة بالدايكلوفيناك صوديوم فقط او مع الباراسيتامول لمدة شهر واحد نتج عنه وعلى التوالي نقصان بالهيموغلوبين التراكمي بنسبة 9.4% و 11.4% ونقصان بمستوى البروتين المتفاعل من نوع سي بنسبة 62.1% و 79.6% و زيادة بنسبة السي بيبتايد 262.5% و**

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216% ونقصان في مستوى السكر عند الصوم بنسبة 11.2% و18.1% ونقصان بمستوى السكر العشوائي بنسبة 40.3% و 24.8% مقارنة بمستوى ما قبل العلاج.

واظهر قياس الهوما–بيتا للسي بيبتايد في عدد محدود من المرضى الذين عولجوا بالدايكلوفيناك أو الدايكلوفيناك مع الباراسيتامول زيادة بنسبة 405.3% و 330.6% وذلك عندما تم قياسها بعد شهرين من ايقاف العلاج.

الاستنتاج: **يبدو ان المعالجة بالدايكلوفيناك صوديوم كبسول 100ملغم ذات التحرير البطئ مرة واحدة يوميا لمدة شهر واحد كان فعالا في الحصول على سيطرة سكرية جيدة لدى مرضى السكري من النوع الثاني غير المسيطر عليه. ولم يكن للباراستامول تأثير واضح في تعزيز تأثير الدايكلوفيناك على الرغم من تأثير الباراسيتامول المفيد الذي أظهرته دراسة سابقة.**

INTRODUCTION

The prevalence of type-2 diabetes mellitus (T2DM), is increasing worldwide, and the total number of people with T2DM is estimated to rise to 526 millions in 2030.[1] In a study published in 2008, the prevalence of T2DM in Basrah (Iraq) was reported to be 7.43%.[2] Both obesity and T2DM share a metabolic event characterized by insulin resistance and chronic inflammation.[3] Chronic inflammation causes insulin resistance by interfering with insulin receptor signaling. Chronic inflammation through proinflammatory cytokines is one of the major factors for progressive loss of beta cell function and mass.[4] Therefore, the use of non-steroidal anti-inflammatory drugs (NSAIDs) may contribute to the treatment of T2DM through these mechanisms. Abdullah[5] studied the effect of diclofenac sodium in 54 patients with T2DM not achieving target HbA1c and found it beneficial in significantly reducing HbA1c level in the majority of patients recruited for that study. However, Khathem et al[6] in a similar study and a smaller number of patients found a significant effect on fasting serum glucose but not on HbA1c after 60 days of treatment. Oxidative stress, on the other hand, had been described to play a major role in the pathogenesis of diabetes mellitus; both in its onset and complications.[7,8] Insulin resistance was linked to oxidative damage of essential macromolecules in insulin sensitive tissues.[9] Prolonged exposure to hyperglycemia and impairment of oxidant/antioxidant equilibrium can result in oxidative stress which can, in turn, lead to beta cell dysfunction and decreased insulin secretion.[10] Thus, oxidative stress and hyperglycemia can reinforce each other. Several studies have suggested that many of these off-label applications of paracetamol such as its beneficial effect on blood glucose levels, may be derived from its ability to function as antioxidant.[11-15] We had already tested the effect of paracetamol 1000mg daily for one month and found it effective in reducing HbA1c level two months after cessation of paracetamol treatment.[16] The aim of the present study is, therefore, to investigate the effect of paracetamol (as antioxidant) when used in combination with diclofenac sodium (as anti-inflammatory) on the glycemic control of patients with T2DM.

PATIENTS AND METHODS

Diabetic patients consulting the Center for Diabetes and Endocrinology in Maysan (south-east of Iraq) during the period from November 2012 to April 2013 were included after meeting a set of inclusion criteria. The study protocol was approved by the College Council and Ethical Committee at the College of Medicine, University of Basrah (south of Iraq). The study is open-label, therapeutic, outpatient-based study to compare one-month treatment with diclofenac sodium alone or in combination with paracetamol on the glycemic control of diabetic patients. All patients were selected during their consultation to the Center for Diabetes and Endocrinology in Maysan. T2DM Patients not achieving target HbA1c level, previously diagnosed for more than one year, age between 30-60 years, no associated cardiovascular diseases, body mass index is 25 or more, on oral antihyperglycemic drugs (both sulfonylureas and metformin) for not less than 6 months, FPG is 126 mg/dl or more, RPG is 200mg/dl or more and HbA1c is 7% or more, no contraindication to the use of paracetamol or NSAIDs, not using aspirin or other anti-inflammatory drugs for at least 2 weeks before being included in the study. Patients were randomly divided into two groups according to

the type of treatment. Randomization lists, one for males and one for females, were prepared in blocks of 10 (5 patients for each treatment). Diclofenac sodium (Voltaren, Mepha, Switzerland), 100 mg SR capsule and paracetamol (Doliprane, Sanofi, France), 1000mg tablet as single daily doses in the morning after meal were used. Because the gastrointestinal adverse effects of NSAIDs may occur without symptoms in the majority of patients, the proton pump inhibitor (Omeprazole, 20mg before meal in the evening) was prescribed to all patients receiving diclofenac sodium. Patients were seen every 2 weeks in the first month to receive the treatments, to check for compliance and to question them about possible side effects. Plasma glucose level (fasting or random) and other laboratory investigations were also done in the meantime. Lipid profile, liver function tests, renal function tests were performed for all patients before starting treatments; and renal function tests were also followed 2 weeks after treatments. All patients were already receiving metformin (Merck, France), 850mg twice daily and glibenclamide (Sanofi-Aventis, France), 5mg daily provided to them by the Center. SPSS (Statistical Package of Social Sciences) version 20 was used for statistical analysis. Paired t test was used to test significance of changes at 0, 1 and 3 months after the start of treatments.

RESULTS

Characteristics of the patients

Out of the 63 type-2 diabetic patients recruited for this study, 45 managed to complete the three month-period of the study. The remaining 18 patients (8 from diclofenac group and 10 from the group of diclofenac and paracetamol) were not able to complete the study and had defaulted at various times of the study. The main reasons for defaulting seem to be attributed to the requirement for frequent visits and blood sampling and the far distance of their residence. Patients in the control group were selected using the same inclusion criteria and found fairly comparable with that of the study groups in terms of age, duration of diabetes, HbA1c% and other parameters (Table-1).

Table 1. Characteristics of patients recruited for this study

Groups	No.	Age (Mean years ± SEM)	Male: Female Ratio	BMI Kg/m^2		Duration of DM (Mean years ± SEM)	Family history		HbA1c level Mean ± SEM
				Over - weight (25-29)	Obese > 30		+ ve	- ve	
Diclofenac sodium	24	50 ± 1.2	0.33 (6:18)	41.7%	58.3%	5.3 ± 0.48	50%	50%	8.5 ± 0.25
Diclofenac + paracetamol	21	50.3 ± 1.7	0.3 (5:16)	71.4%	28.6%	5.1 ± 0.56	66.7%	33.3%	8.58 ± 0.2
Control	60	46.5 ± 0.78	0.53 (21:39)	73%	27%	4.1 ± 0.28	56.7%	43.3%	8.1 ± 0.1

2. The effects of one month treatment with diclofenac sodium 100mg SR capsule once daily on type-2 diabetic patients not achieving target HbA1c (n=24).

HbA1c level before starting treatment with diclofenac was 8.5 ± 0.25%. This was reduced by only 2.35% after one month of diclofenac treatment. However, a statistically significant reduction (by 9.41%, P = 0.017) was achieved two months after stopping diclofenac treatment.

The CRP was reduced significantly by 50.5% one month after the start of diclofenac treatment (P=0.063). Slightly more reduction occurred two months after cessation of diclofenac treatment (Table-2).

C-peptide level increased significantly by 93.8% after one month of treatment with diclofenac sodium (P < 0.001). This increase became more clear two months after cessation of diclofenac treatment (an increase by 262.5%, P < 0.001).

There is an insignificant reduction in FPG by 10.4% and 11.2% after one and three months after the start treatment with diclofenac sodium respectively.

There is a statistically significant reduction in random plasma glucose by 22.8% (P < 0.001)

after one month of diclofenac treatment. This reduction continued to increase two months after cessation of diclofenac treatment 40.3%**.**

3. The effects of one month treatment of diclofenac sodium 100mg SR capsule and paracetamol 1000mg tablet once daily on type-2 diabetic patients not achieving target HbA1c (n=21).

The mean ± SEM of HbA1c before the start of treatment is (8.58 ± 0.2). This had been reduced to (8.38 ± 0.34) after one month of treatment with the combination (a reduction by 2.33%, P = 0.475). HbA1c levels continued to decrease two months after stopping treatment reaching a level of (7.6 ± 0.024) a significant reduction by 11.4%, P < 0.001 (Table-2, Figure-1).

CRP decreased by 2.72%, after one month treatment with the combination but this reduction is not significant (P = 0.96). However, two months after stopping treatment, CRP continued to decrease reaching a level of 3±0.25 (a reduction by 79.6%, P = 0.064).

C-peptide level is increased significantly by 113.2% one month after treatment. The C-peptide level continued to increase two months after cessation treatment (an increase by 216%, P < 0.001)

FPG level was significantly reduced but only by 14.2% and 18.1% one and three months after the start of treatment respectively (Table-2).

Random plasma glucose after one month treatment is reduced significantly by 17.3% (P = 0.002). Two months after stopping treatment random plasma glucose continued to decrease and it was 24.8% less than pre-treatment level (P = 0.002)**.**

Table 2. Comparison between the effect of diclofenac sodium, and the combination of diclofenac and paracetamol on different parameters, presented as percent change in comparison to pre-treatment measurements.

Parameters	Month(s) after starting treatment	Treatment groups (% change with respect to pre-treatment level)	
		Diclofenac sodium N = 24	Diclofenac sodium with paracetamol N = 21
HbA1c	1	↓2.35%	↓2.33%
	3	↓9.4%*	↓11.4%*
CRP	1	↓50.5%*	↓2.72%
	3	↓62.1%*	↓79.6%*
C-peptide	1	↑93.8%*	↑113.2%*
	3	↑262.5%*	↑216%*
FPG	1	↓10.4%	↓14.2%*
	3	↓11.2%	↓18.1%*
RPG	1	↓22.8%*	↓17.3%*
	3	↓40.3%*	↓24.8%*

***Statistically significant difference compared with pre-treatment levels**

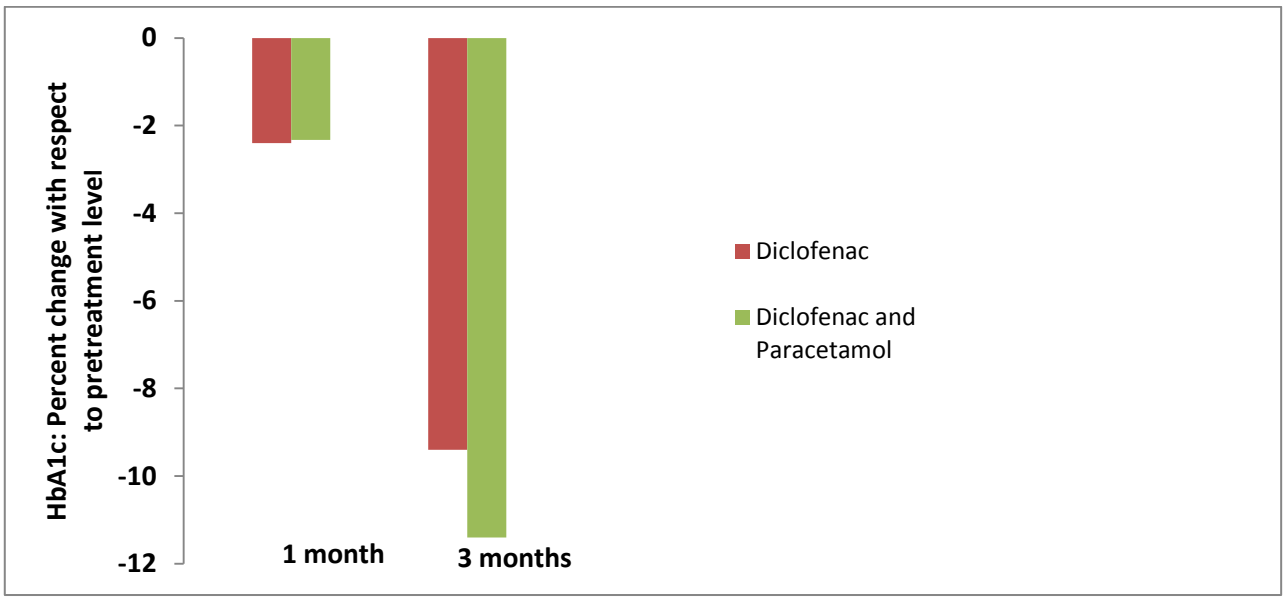

Fig 1. The effect of diclofenac sodium alone or in combination with paracetamol on HbA1c level, presented as percent change with respect to pre-treatment measurements.

No significant changes were found in the control group over the three months of the study period as to the level of HbA1c, FPG, and RPG when measured at one and three months compared with zero time.

DISCUSSION

Inflammation can cause or increase insulin resistance as well as insulin deficiency.[17] The source of the inflammatory mediators are cells like adipocytes and macrophages. Markers such as CRP and IL-6 are found to be elevated in type 2 diabetes.[18] Therefore, the reduction in these inflammatory reactions may help in improvement of glycemic control in DM.[19] Obese diabetic patients with BMI > 25 where they are expected to have chronic inflammatory states, were included in the present study. The non-steroidal anti-inflammatory drug; diclofenac sodium 100mg daily orally was given to these diabetic patients who were not achieving target HbA1c. It resulted in a significant reduction in HbA1c level by 9.41% two months after cessation of diclofenac treatment. Diclofenac sodium as an anti-inflammatory drug is expected to reduce the level of CRP which was significantly reduced at the end of one month treatment and two months later. C-peptide was increased significantly after one month of diclofenac treatment (by 93.8%) and two months later (by 262.5%). These two mechanisms (anti-inflammatory effect and increased release of insulin) might be responsible for the favorable effect of diclofenac on HbA1c level and on RPG but probably not on FPG. This might indicate that diclofenac is more effective when plasma glucose is high such as that occurring postprandially. Khathem *et al*[6] studied the effect of diclofenac sodium 50mg twice daily for 2 months on poorly controlled T2DM. They found a significant effect on FPG, but not on HbA1c levels. However, the sample size in their study is only 12 (2 males and 10 females). The small sample size might be responsible for not detecting any potential effect of diclofenac sodium on HbA1c. Abdullah[5] in Basrah, Iraq also studied the effect of diclofenac sodium (100mg once daily) on 54 type 2 diabetic patients not achieving target HbA1c. The study resulted in a statistically significant reduction in HbA1c level by 10.9% after one month treatment with diclofenac sodium and 19.9% two months later. Similar effect of diclofenac on fasting and post-prandial plasma glucose levels was found. The results of the present study and that of Abdullah 2013 are in the same direction although they differ slightly in the extent of effect particularly on HbA1c levels, probably due to larger sample size (54 patients compared to 24 patients in the present study). The reduction in HbA1c obtained in the present study and in the study of Abdullah[5] is higher

than that previously reported using another NSAID; salsalate. In a recent study, salsalate, when administered in dosages of 3.5g/d for 48 weeks, reduced HbA1c levels by 0.37% compared with a placebo group.[20] The comparison in the latter study is with a placebo group rather than with pre-treatment level as in the present study. Again, and as reported by Abdullah,[5] the effect of diclofenac became more clear two months after cessation of diclofenac treatment. This delayed effect seems to be consistent in the two studies. However, it may point to a significant impact, inflammation has on the glycemic control and on insulin action. All diabetic patients in the present study were on treatment with oral antihyperglycemic drugs; both metformin and a sulfonylurea. Therefore, an interaction between diclofenac sodium and the oral antihyperglycemic drugs cannot be excluded since diclofenac and sulphonylureas are both highly protein bound. Diclofenac can displace glibenclamide from its protein binding site and enhance its effect.[21] Sone et al[22] found that this effect of NSAIDs is often seen in diabetic patients receiving sulfonylureas. Similarly, antihyperglycemic drugs can also reduce CRP levels.[23] CRP was decreased significantly by 50.5% one month after diclofenac treatment and this reduction is increased 62.1% two months after cessation of treatment. Again, the possible interaction between diclofenac sodium and oral antihyperglycemic drugs might contribute to the sustained effect on CRP and other parameters two months after cessation of diclofenac treatment. Oxidative stress is one of the factors that lead to T2DM, and it, in association with hyperglycemia, can reinforce each other.[24] The increase in antioxidant capacity may, therefore, help in improving glycemic control in DM.[25] Several experimental and clinical studies suggest that paracetamol (acetaminophen) can improve blood glucose level; an effect that might result from its antioxidant properties.[26,27] Moreover, several studies have suggested that the off-label applications of paracetamol may be derived from its ability to function as antioxidant.[11-15] Because there is a positive feedback between inflammation and oxidative stress, [28] the effect of combining paracetamol (as a potential antioxidant) and diclofenac sodium (as anti-inflammatory) on the parameters measured had been studied. These two drugs are frequently prescribed to the patients in clinical practice. The results showed that there was no clear additive or synergistic effect of the combination compared with the effect of each drug given individually. Three months after the start of treatment, the combination caused a slightly increased effect on HbA1c. Similar results were found with CRP and FPG. The use of omeprazole is to overcome the ethical issue of diclofenac-induced GI side effects. However, it represents a confounding factor since it is used with diclofenac but not with paracetamol. Fortunately, omeprazole as enzyme inhibitor affects the metabolism of diazepam, warfarin and clopidogrel which are metabolized by CYP2C19 and CYP2C9, but not that of diclofenac and paracetamol.[29,30] The effect of proton pump inhibitors on HbA1c and glycemic control is controversial. Most of the studies that have reported a beneficial effect of omeprazole on HbA1c are not controlled, randomized clinical trials. A recent randomized, double-blind prospective, placebo-controlled study of the proton pump inhibitor (esomeprazole) for 12 weeks found no improvement in glycemic control or insulin secretion in patients with type 2 diabetes.[31] The findings in the present study indicate that paracetamol did not add much to diclofenac beneficial effect inT2DM.

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