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The Potential Therapeutic Benefit of Diclofenac Sodium in Treatment of Patients with Type-2 Diabetes Mellitus

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AMJ and AAM designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author NAA gave the treatment and followed the patients. All authors read and approved the final manuscript.

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ABSTRACT

Background: Type-2 diabetes mellitus, is associated with low-grade chronic inflammation, which could contribute to its pathogenesis. The objective of this study is to evaluate the role of the non-steroidal antinflammatory drug (diclofenac sodium) in type 2 diabetic patients who are not achieving target HbA1c.
Patients and Methods: Fifty four, type-2 diabetic patients consulting Al-Faiha Diabetes, Endocrine and Metabolism Center (FDEMC) in Basrah were included in this study after meeting a set of inclusion criteria. Their HbA1c was more than 7% (53 mmol/mol) despite the optimal use of oral antihyperglycemic drugs. They were overweight with a BMI of 25 or more. They served as the study group and treated with diclofenac sodium. Diclofenac sodium was administered to each patient as 100 mg sustained-release capsule, given once daily for one month (with omeprazole 20 mg daily). Another fifty patients of similar inclusion criteria were also followed for 3 months, but without treatment with diclofenac sodium and served as a control group.
Results: Treatment with diclofenac sodium 100 mg sustained-release capsules (in presence of

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omeprazole 20 mg daily), resulted in a significant improvement in the glycemic control and inflammation parameters in the form of a reduction in the HbA1c, fasting plasma glucose and postprandial plasma glucose. The mean ± SEM of HbA1c before the start of treatment with diclofenac sodium is 9.26±0.269 percentage which was reduced significantly to 8.25 ± 0.255 percentages after one month of diclofenac treatment (a reduction by 10.9%, p<0. 001). HbA1c levels continued to decrease even after stopping diclofenac treatment reaching a level of 7.41% (a reduction of 19.9% compared to pre-treatment level, p <0. 001). Fasting plasma glucose decreased significantly from a mean ± SEM of 153.87±4.65 mg/dl to 129.98±3.41 mg/dl (a decrease of 16%, p<0. 001). *High-sensitivity C-reactive protein* also decreased by 19% one month after diclofenac treatment. Two months after stopping treatment, *high-sensitivity C-reactive protein* continued to decrease reaching a value of 0.379±0.291 mg/L (a reduction by 45%, p<0. 001). There was no significant change in insulin level after diclofenac treatment. Insulin resistance, measured by the Homeostasis Model of Assessment - Insulin Resistance (HOMA-IR) equation, decreased two months after diclofenac treatment from 83.3% to 68.5%.

Conclusion: If the results of this study are confirmed by other studies in the future,type-2 diabetic patients who are not achieving target HbA1c after treatment with two oral antihyperglycemic drugs, showed a significantly reduced HbA1c levels compared with pre-treatment levels when treated with diclofenac sodium 100 mg SR capsule for one month, with no side effects. This reduction, increased further even after cessation of diclofenac treatment with reduction in the markers of insulin resistance and inflammation.

Keywords: Type 2 diabetes; insulin resistance; inflammation; diclofenac sodium.

1. INTRODUCTION

Inflammation can lead to type-2 diabetes by causing or exacerbating insulin resistance and insulin deficiency. Chronic inflammation causes insulin resistance by interfering with insulin receptor signaling [1]. Similarly, chronic inflammation impairs beta-cell function and induces beta-cell death, leading to a progressive decline in beta-cell mass [2].

Once diabetes is established, chronic hyperglycemia exacerbates inflammation through the production of free radicals and reactive oxygen species [3]. Normally, glucose metabolism results in the production of a small amount of reactive oxygen species. These toxic molecules are removed by endogenous antioxidant defense mechanisms. In diabetes mellitus, increased glucose metabolism results in increased production of reactive oxygen species. The endogenous antioxidant defenses are exhausted, allowing free radicals and reactive oxygen species to directly damage beta-cells [3]. The inflammatory cytokines are derived primarily from macrophages, which infiltrate the adipose tissue in obese to remove dying cells and can directly enhance insulin resistance in adipocytes, muscle and liver cells [4].

This study aims to evaluate the role of the diclofenac sodium, as anti-inflammatory agent, in patients not achieving the target HbA1c with two oral antihyperglycemic agents.

2. PATIENTS AND METHODS

One hundred and four diabetic patients consulting Al-Faiha Specialized Diabetes, Endocrine, and Metabolism Center (FDEMC) in Basrah (54 patients in the study group and 50 the control group) during the period from November 2011 to August 2012 were included after meeting a set of inclusion criteria. The study protocol was approved by the College Council and implicitly by the Ethical Committee of the College of Medicine, University of Basrah, Iraq.

2.1 Ethical Consideration

All participants were informed about the aim of the study and were asked for their permission before taking the blood samples. Informed consent taken from each patient. Personal data were considered confidential and were used only for statistical analysis.

2.2 Inclusion Criteria

Patients with type 2 diabetes diagnosed for more than one year.

No associated cardiovascular diseases by history and clinical examination

Age: 30-60 years

Males and non-pregnant females

Body mass index is 25 kg/m^2 or more

On oral hypoglycemic drugs (both metformin and glibenclamide, maximum dose for at least 6 months)
Glycated hemoglobin test (HbA1c) 7% (53 mmol/mol) and above.

2.3 Exclusion Criteria

Body mass index <25 kg/m^2
Any contraindications to use of nonsteroidal anti-inflammatory drugs (*NSAIDs*): present history of peptic ulcer, impairment of hepatic and renal functions, bleeding tendencies, severe hypertension (systolic blood pressure of 180 mm Hg or greater, or diastolic blood pressure of 110 mm Hg or greater), heart failure, allergy to aspirin or any *NSAIDs*, asthma, angioedema and on drugs like anticoagulants.

2.4 Laboratory Investigations

Each recruited patient was exposed first to the following investigations: liver function tests, renal function tests, HbA1c, and fasting plasma glucose (FPG), *high-sensitivity C-reactive protein* (*hsCRP*) and insulin. All these tests were done in the laboratory of FDEMC. Blood samples were taken from all patients before, one month and 3 months after diclofenac administration, except for FPG, where it measured before, after 1, 2 and 3 months. Plasma glucose concentrations were measured using an automated glucose oxidase method (Biolyzer ® 300; Analyticon Biotechnologies AG, Lichtenfels, Germany). HbA1c levels of the patients were measured using a Bio-Rad D-10 HPLC instrument (UNITED STATES, Bio-Rad Laboratories, Inc., Hercules, CA 94547). HsCRP and insulin was measured by ELISA –DRG (Germany). The normal reference range 2 µIU/ml to 25 µIU/ml. The range of the assay is between 1.76 – 100 µIU/ml with specified the intra-assay precision of mean 17.5 µIU/ml (2.6 % CV).

2.5 Drug Treatment

In this open-label, therapeutic, outpatient-based study, patients were instructed to take a single oral daily dose of diclofenac sodium 100 mg SR capsule in the morning after meal for one month. Capsules were marked on the back of the sheet according to the days of the week to encourage compliance. Proton pump inhibitors are prescribed for each patient in form of omeprazole 20 mg daily given in the early morning throughout the study period to reduce the side effect of the drug.

2.6 Follow Up

During the one-month treatment with diclofenac, patients were asked to visit the center every 10 days for follow up, to measure FPG. At the end of one-month diclofenac treatment, another blood sample was withdrawn from the patients for measurement of HbA1c, FPG, insulin level and C-reactive protein. Two months after treatment with diclofenac sodium had been stopped, HbA1c, insulin level and *hsCRP* measurements were repeated. A checklist for adverse effects was used to detect any potential adverse event occurring during and after diclofenac treatment.

2.7 Non-diclofenac Control Group

A group of type-2 diabetic patients consulting the diabetic center were matched for age, gender, BMI and response to antihyperglycemic treatment with the intervention group (HbA1c ≥ 7% - 53 mmol/mol despite receiving the two oral anti-hyperglycemic drugs i.e. metformin and glibenclamide). They were also followed for changes in HbA1c and plasma glucose over 3 months to test for the time effect on the level of HbA1c without diclofenac sodium treatment.

HOMA-IR values (Homeostasis Model of Assessment - Insulin Resistance)

HOMA-IR values are calculated according to the following equation:

HOMA1-IR = fasting plasma glucose (mg/dl) x fasting Insulin (µU/ml) / 405 [5].

2.8 Statistical Analysis

Comparisons between before and after diclofenac treatment and between different groups according to their level of HbA1c were determined by analysis of variance (ANOVA) using SPSS (Statistical package for the Social Sciences) version 15. Paired t-test was used to test the significance of changes in 0, 1 and 3 months after treatment. A difference was considered statistically significant for p value of 0.05 and less.

3. RESULTS

Out of 65 diabetic patients recruited in this study, 54 completed the 3 month study. Eleven patients were not able to complete the study and had defaulted at various times of the study. An interview with three defaulters showed that the

main reason for defaulting was attributed to the requirement for frequent visits and blood sampling. Patients in the control group were selected using the same inclusion criteria and found fairly comparable with that of the study group in terms of age, duration of diabetes, HbA1c % and FPG (Table 1).

The mean ± standard error of the mean (SEM) of HbA1c before the start of treatment with diclofenac sodium is 9.26±0.269 percent. This had been reduced significantly to 8.25 ± 0.255 percent after one month of diclofenac treatment (a reduction by 10.9%, p<0. 001). HbA1c levels continued to decrease even after stopping diclofenac treatment reaching a level of 7.41% (a reduction of 19.9% compared to pre-treatment level, p <0. 001) (Fig. 1).

HhsCRP decreased by 19% one month after diclofenac treatment. This decrease is not statistically significant. However, two months after stopping treatment, *hsCRP* continued to decrease reaching a value of 0.379±0.291 mg/L (a reduction by 45%, p<0. 001, Fig. 2).

Insulin level did not change significantly after one month – treatment with diclofenac sodium or two months after stopping the treatment when compared with its level before diclofenac administration. The means of pre-treatment and one and three months after treatment were 23.12, 21.77 and 19.31 µUnit/ml respectively (Table 2).

FPG decreased significantly from a mean ± SEM of 153.87±4.65 mg/dl to 129.98±3.41 mg/dl (a decrease of 16%, p<0. 001) and remained at that level in the following measurements (Table 3).

PPG was also compared before diclofenac treatment with three readings during and after diclofenac treatment. The mean ± SEM of PPG before treatment in a limited number of patients was 195.25±10.59 mg/dl (n = 24). This was reduced significantly by (15.5%, P<0. 05) to 165.13±6.43 mg/dl, and from 197.36±11.3 mg/dl (n =22) before diclofenac administration to 156.1±6.43 (p = 0.003).

3.1 Non-diclofenac Control Group

Fifty type-2 diabetic patients with poor glycemic control and of similar inclusion criteria as the intervention group (n=54) were followed for 3 months. They were taking their conventional treatment, both metformin and the sulphonylurea (glibenclamide). Their HbA1c did not change over the 3-month period (9.61±1.7 and 9.51±1.84 percent at 0 and 3 months respectively) (Table 4).

3.2 HOMA-IR Index of the 54 Patients Treated with Diclofenac Sodium 100 mg SR Capsules Once Daily for One Month

The HOMA-IR index of each of the 54 diabetic patients was calculated according to an equation relating fasting plasma glucose and fasting insulin level. Because no cutoff point is yet agreed upon in the literature above which insulin resistance is diagnosed, two reported cutoff points were taken in the present study; the lowest is 1.67 and the highest is 4. Out of the 54 diabetic patients, 83.3% and 64.8% were found to have insulin resistance, according to the two cutoff points respectively (Table 5) [5]. These proportions of insulin resistant patients decreased slightly at the end of the diclofenac treatment period.

Table 1. Characteristics of patients in the study group (receiving diclofenac sodium 100 mg SR capsule, once daily, in addition to the oral antihyperglycemic drugs) and control group (receiving oral antihyperglycemic drugs only)

Parameters	Study group (n=54)	Control (n = 50)	P value
Age (Years; mean ± SEM)	49.15±0.87	45.52±0.93	NS
Male/female ratio	20/34 (0.59)	23/27 (0.85)	NS
Duration of diabetes (years; mean± SEM)	4.37±0.29	4.28±0.27	NS
HbA1c % (Mean ± SEM)	9.26±0.27	9.61±0.26	NS
BMI (kg/m2) (overweight/obese) ratio	17/37(0.46)	14/36 (0.39)	NS
FPG mg/dl (mean± SEM)	153.87±4.65	158.41±3.54	NS

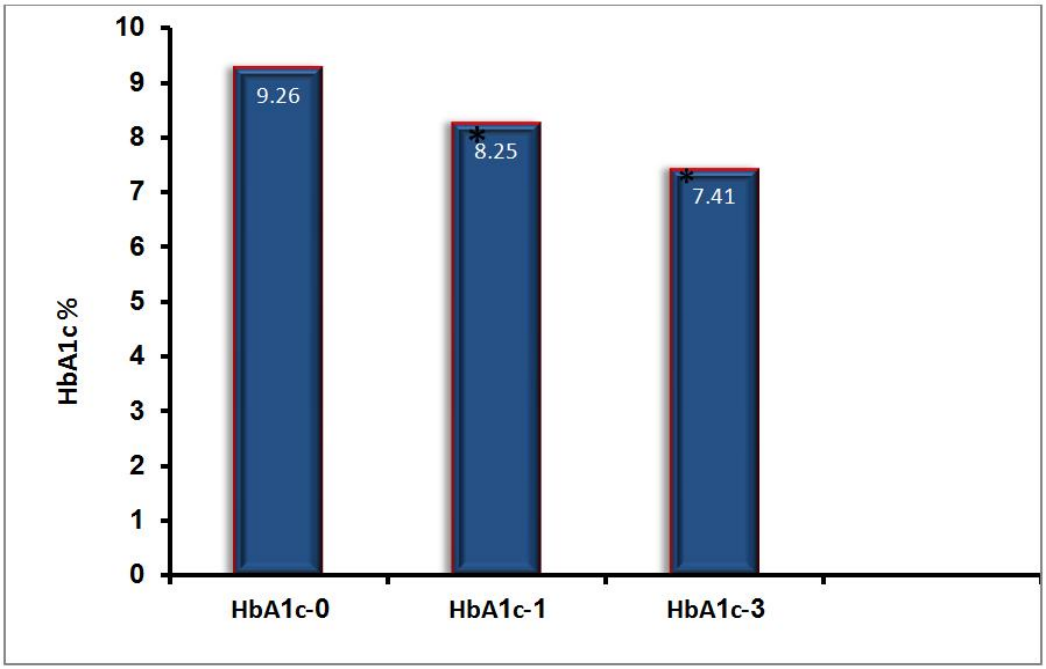

Fig. 1. HbA1c level before, 1 and 3 months after the start of treatment of type-2 diabetic patients with diclofenac sodium 100 mg once daily for one month

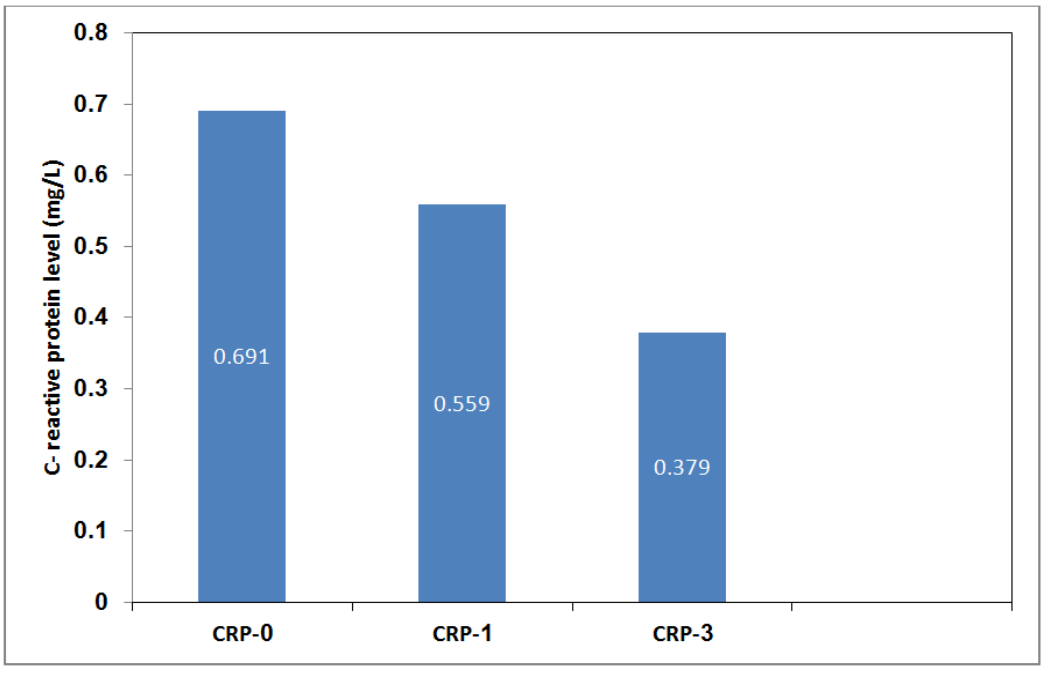

Fig. 2. hs C-reactive protein before, one month (CRP-1) and three months (CRP-3) after treatment of type-2 diabetic patients with diclofenac sodium 100 mg SR capsule once daily

The difference between CRP-0 and CRP-1 was no significant. The p value for difference between CRP-1and CRP-3 was p<0. 001

Table 2. Insulin blood level before and 1 and 3 months after the start of treatment of type-2 diabetic patients with diclofenac sodium 100 mg SR capsule once daily for one month

Time with respect to diclofenac treatment	Number of patients	Insulin level (µUnit/ml)	SEM	* P value
Pre-treatment	54	23.12	3.25	
One month after treatment	54	21.77	2.52	P=0.48
3 months after	54	19.31	2.41	P=0. 125

**Significant difference with respect to pre-treatment level*

Table 3. Fasting plasma glucose (FPG) before, during and after the start of treatment of type-2 diabetic patients with diclofenac sodium 100 mg SR capsule once daily for one month

Time with respect to diclofenac treatment	Number of patients	Mean FPG (mg/dl)	SEM	% change to before treatment	*P value
Pre treatment	54	153.87	4.65	-	
1st reading after	54	129.98	3.41	↓ 16%	P<0.001
2nd reading after	54	123.19	3.60	↓ 19.9%	P<0. 001
3rd reading after	54	124.19	3.54	↓ 19.3%	P<0. 001

**Significant difference with respect to before treatment level*

Table 4. HbA1c of the no-diclofenac control group with other characteristics of the patients (n=50)

HbA1c at 0 times (%)	HbA1c at 3 months (%)	Age (year)	Gender	BMI
9.61±0.26	9.51±0.24	45.52±0.93	23 males 27 females	14 overweight 36 obese

Data are presented as means ±SEM of n = 50 patients

Table 5. The number of patients showing insulin resistance calculated according to two HOMA-IR cutoff points, before and after treatment with diclofenac sodium 100 mg SR capsules for one month (total number of patients is 54)

HOMA-IR cutoff points		Before diclofenac treatment	After diclofenac treatment	
			1 month	3 months
1.67	≥ 1.67	45 (83.3%)	43 (79.6%)	37 (68.5%)
	<1.67	9 (16.7%)	11 (20.4%)	17 (31.5%)
4	≥ 4	35 (64.8%)	33 (61.1%)	28 (51.9%)
	< 4	19 (35.2%)	21 (38.9%)	26 (48.1%)

Data are expressed as the number of patients (% of the total 54 patients).P value=0.086

However, two months after stopping diclofenac treatment, more insulin resistant patients became insulin sensitive (16.7% insulin sensitivity increased to 31.5% two months after diclofenac treatment at the cutoff point of 1.67). These changes just failed to reach statistical significance (statistical significance three months after the start of treatment with respect to pre-treatment level; p =0. 086).

4. DISCUSSION

The vast majority of patients with type 2 diabetes show insulin resistance, which usually occur before the first symptoms of the disease [6]. In the present study, overweight diabetic patients (BMI ≥25) were studied since adipocytes and other cells are the main source of inflammatory mediators in obese patients. The non-steroidal anti-inflammatory drug; diclofenac sodium 100 mg daily orally, resulted in a statistically significant reduction in HbA1c level by 10.9% after one-month treatment of the 54 diabetic patients taken as one group (Table 3.2). Similar effect of diclofenac treatment on fasting and random blood sugar levels was found.

Khathem et al. in 2006 [7] also studied the effect of diclofenac sodium 50mg twice daily for 2 months on poorly controlled type-2 DM. Although they found a significant effect of FPG levels,

there was no significant effect on HbA1c levels. The sample size in their study is only 12 (2 males and 10 females), and this small sample size might be responsible for not detecting any potential effect of diclofenac sodium on HbA1c levels.

Van Erk et al. [8] had given diclofenac to 50 apparently healthy over-weight individuals for 9 days. Diclofenac had not been shown to cause changes in a wide range of inflammatory markers. CRP changed in the placebo group rather than in diclofenac group. However, 9-day treatment might be too short for the optimal anti-inflammatory effect of diclofenac, which requires 2 to 3 weeks to accomplish. In addition, the subjects used in their study were apparently healthy.

In another study by Schlumpf [9] on patients with type-2 DM, no effect of diclofenac sodium on glucose metabolism was found whether the patients on diet only or diet and tolbutamide. The sample size was also small (13 to 14 in each group).

The reduction in HbA1c obtained in the present study is higher than that previously reported using another NSAID; salsalate. Salsalate reduced HbA1c levels by about 0.5% from baseline when administered in dosages of 4.0 g/d for 14 weeks. Other measures of glycemic control such as fasting blood glucose and glycated albumin were also reduced [10].

Surprisingly, HbA1c levels as an average of the 54 patients as a whole continued to show a decrease over the 2 months after stopping diclofenac treatment from around 10% to 20% compared with pre-treatment levels. The level of HbA1c is supposed to be stable over the life span of the RBCs (about 3 months). The significant reduction of HbA1c after one month of diclofenac treatment is, therefore, difficult to explain. More difficult is the continued reduction over the next two months, despite stopping diclofenac treatment. If this sustained effect is proved to be true, it could point to the significant impact inflammation might have on the glycemic control and insulin action. Technical error in measuring HbA1c might not be a factor since it had been measured using automated HPLC equipment and its reproducibility had been tested several times. Similarly, none of the factors that might result in a decrease in HbA1c level, such as blood transfusion and high red blood turnover [11] could be found.

All the 54 patients were on full treatment with oral antihyperglycemic drugs; both metformin and sulfonylurea (glibenclamide). It is quite possible that this large reduction in HbA1c is the result of interaction between diclofenac sodium and the oral hypoglycemic drugs. NSAIDs can affect ion channels in insulin secreting beta cells and induce hypoglycemia. Sone et al. [12] found that this effect of NSAIDs is often seen in diabetic patients receiving sulphonylurea.

In this study the CRP decreased by 19% one month after diclofenac treatment. This decrease is not statistically significant. However, two months after stopping treatment, CRP continued to decrease reaching a value of 0.379 ± 0.291 (a reduction by 45%, $p<0.001$). Anti-diabetic agents can also reduce CRP levels [13]. As cited above, the interaction between diclofenac sodium and oral hypoglycemic drugs might be responsible for the sustained effect on CRP two months after stopping diclofenac treatment.

To overcome the ethical issue of diclofenac-induced GI side effects, omeprazole is used in this study, although it represents a confounding factor since it is used only with diclofenac.

There are variable effects of proton pump inhibitors on HbA1c and glycemic control. However, 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 [14].

Aspirin low doses (between 81 and 100 mg/day) failed to decrease CRP levels. This might suggest that anti-platelet doses of aspirin may not influence CRP production. Treatment with other anti-inflammatory drugs, such as cyclooxygenase-2 (COX-2) inhibitors can support that anti-inflammatory therapies lower CRP levels [15].

Diet is another confounding factor. The diet of the patient is generally controlled according to printed instructions given to the patients during their visits to the center. The presence of a control group may help in reducing the effect of this variable.

It is known that NSAIDs, including diclofenac, can suppress TNF-α and CRP [16]. TNF-α is important in the development of insulin resistance. It is produced more than 7 times by

adipose tissue in obese subjects compared to lean subjects [17]. The present study on both obese and overweight patients, showed that diclofenac can play an important role in the reductions of inflammatory markers such as CRP.

Insulin resistance is important in the development of type 2 diabetes mellitus. Using HOMA-IR, a large number of subjects can be studied with a single fasting glucose and insulin measurement [18]. In the present study, most of the 54 patients had insulin resistance. Treatment with diclofenac sodium for one month in such patients improved insulin sensitivity in 12.9%, and in 14.8% two months after stopping the treatment. This might indicate that the response to diclofenac could partly be attributed to improved insulin sensitivity.

It is, therefore, concluded that patients not achieving target HbA1c on two oral antihyperglycemic drugs when treated with diclofenac sodium 100mg SR capsule for one month, showed a significantly reduced HbA1c levels compared with pre-treatment levels. This reduction, increased further even after stopping diclofenac treatment with reduction in the markers of insulin resistance and inflammation.

5. CONCLUSION

If the results of this study are confirmed by other studies in the future, type-2 diabetic patients who are not achieving target HbA1c after treatment with two oral antihyperglycemic drugs, showed a significantly reduced HbA1c levels compared with pre-treatment levels when treated with diclofenac sodium 100 mg SR capsule for one month, with no side effects. This reduction, increased further even after cessation of diclofenac treatment with reduction in the markers of insulin resistance and inflammation.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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