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ABSTRACT

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IMPACT OF HIGHLY SELECTIVE VERSUS RELATIVELY SELECTIVE COX2 INHIBITORS ON INSULIN SENSITIVITY IN IRAQI PATIENTS DIAGNOSED WITH TYPE 2 DIABETES

***Background*:** A worldwide health epidemic, type 2 diabetes mellitus was significantly influenced by chronic inflammation, which led to increased insulin resistance (IR). The most widely practiced form of therapy used to control musculoskeletal pain in people with diabetes is non-steroidal anti-inflammatory drugs (NSAIDs), which provide their action by inhibiting cyclooxygenase enzyme (COX). COX1, COX2, and COX3 are distinct isoforms of the cyclooxygenase enzyme. The potential anti-inflammatory benefits of cyclooxygenase-2 (COX-2) inhibitors, both selective and non-selective, have been investigated concerning the management of type 2 diabetes patients.

***Objective*:** the purpose of this research is to explore the impact of highly selective celecoxib and relatively selective diclofenac (COX-2) inhibitors on insulin sensitivity in type 2 diabetes patients.

Methods: A sample of 136 patients with T2DM (92 females, 44 males) and 64 healthy controls (36 females, 28 males) was formed. Two groups of patients, Group 1 (hyperlipidemia) and Group 2 (normolipidemic), were created. Each group received treatment with either diclofenac or celecoxib in half. Insulin sensitivity was ascertained using the quantitative insulin sensitivity check index (QUICKI) formula.

***Results*:** Both normolipidemic and hyperlipidemic diabetics had higher fasting plasma glucose levels (p-value) and lower QUICKI scores compared to the controls. Diclofenac significantly increased serum insulin and decreased fasting glucose in hyperlipidemic diabetics, while celecoxib also reduced fasting glucose and QUICKI scores in hyperlipidemic. In normolipidemic diabetics, diclofenac decreased fasting glucose and increased insulin, whereas celecoxib increased insulin but decreased QUICKI scores.

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***Conclusion*:** Targeted COX-2 inhibitors such as celecoxib may considerably provide valuable benefits, including enhanced insulin sensitivity, metabolic function, and overall health.

Keywords: QUICKI, diclofenac, celecoxib, insulin sensitivity, hyperlipidemia, type 2 diabetes, COX-2 inhibitors.

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INTRODUCTION

The high atherogenicity linked to diabetic dyslipidemia is probably responsible for the characteristic findings of raised levels of triglycerides (TG) and low plasma levels of high-density lipoprotein cholesterol (HDL-C) [1]. The evidence suggests a potential connection between diabetes and cyclooxygenase-2-mediated inflammation. Furthermore, two main types of cyclooxygenase have been identified: COX-1 is expressed constitutively in nearly every tissue. In contrast, COX-2 is engaged in regulating inflammatory responses and is mainly influenced by cytokines and growth factors. While COX-3, a splice variant of COX-1, is primarily found in the heart and brain, highlighting its potential roles in these vital organs [2].

Non-steroidal anti-inflammatory drugs are also referred to as NSAIDs because of their structural differences from steroidal anti-inflammatory drugs. Because NSAIDs work by inhibiting COX activity, they have antipyretic, analgesic, and anti-inflammatory qualities. Celecoxib, rofecoxib, and valdecoxib, however, might work therapeutically similarly to non-specific COX-2 inhibitors without adverse side effects [3]. Relatively selective Cx-2 inhibitors, like diclofenac. Cyclooxygenase-2 (COX-2) activity is selectively inhibited by highly eclectic COX-2 inhibitors, including celecoxib, a non-steroidal anti-inflammatory medication, and rofecoxib [3].

The International Diabetes Federation projects that approximately 415 million adults globally are currently affected by diabetes, with an additional 318 million experiencing impaired glucose tolerance. It is anticipated that these figures will rise to 642 million and 482 million, respectively, by the year 2040. This increasing prevalence presents substantial challenges for nations worldwide, particularly in regions with limited resources [4, 5].

Recent studies have shown that individuals without diabetes who have chronic low-grade inflammation may have a higher risk of type 2 diabetes and a decreased sensitivity to insulin [6, 7]. According to some theories, reducing low-grade inflammation may reduce the risk of type 2 diabetes. The discovery was that salicylates, a class of anti-inflammatory drugs that includes aspirin, influence a specific anti-inflammatory pathway, reduce plasma glucose levels, and enhance insulin sensitivity in type 2 diabetics. Type 2 diabetes mellitus (T2DM) is generally recognized as being associated with chronic inflammation and insulin resistance (IR) [8]. Insulin resistance (IR) has been associated with the inflammatory pathway mediated by cyclooxygenase-2 (COX-2). Due to their anti-inflammatory qualities, COX-2 inhibitors are frequently used. They can be classified as highly selective (like celecoxib) or relatively selective (like diclofenac). This research examines how these two classes of COX-2 inhibitors affect insulin sensitivity in T2DM patients based on their lipid profile (hyperlipidemic versus normolipidemic) [9]. It has been proposed that by lowering inflammation, COX-2 inhibition increases insulin sensitivity. However, it is unclear whether the degree of COX-2 selectivity influences this effect. The research aims to explore the impact of selective versus non-selective COX-2 inhibition on insulin sensitivity in a group of T2DM patients and healthy individuals [10, 11].

The study estimates the influence of highly eclectic and relatively eclectic COX2 inhibitors on the insulin sensitivity of patients with type 2 diabetes in Iraq.

METHODS

Study Population

Our samples included one hundred thirty-six subjects (forty-four males and ninty-two females) with type 2 diabetes and were between the ages of 40 and 55 years and have musculoskeletal pain on oral anti-diabetic drugs (glibene clammide with or without metformin) were included in the study. In contrast, the control group consisted of 64 objects (twenty-eight males and thirty-six females) who appeared to be in good health. Based on their serum lipid profile, the diabetic patients were divided into two groups: The first group comprised 80 diabetic patients with hyperlipidemia. Patients on statins or insulin were excluded from the study.

Treatment Protocol

The dosage was given in accordance with accepted therapeutic guidelines. 200 mg of celecoxib and 100 mg

of diclofenac were given daily. Patients' regular diabetes medications were not altered throughout the trial.

Group 1: eighty hyperlipidemic patients (twenty-eight men and fifty-two women), 52 of whom received an 8-week single-dose treatment of celecoxib (2 mg/day). 28 subjects received a single dose of diclofenac 100 mg/day for a duration of 8 weeks.

Group 2 comprised 56 patients (16 males and 40 females) with normal lipidemia. Twenty-eight of the patients received treatment with celecoxib 200 mg/day for eight weeks, and twenty-eight of the patients received treatment with diclofenac 100 mg/day for eight weeks. Sixty-four subjects in Group 3 (28 men and 36 women appeared to be in good health and were used as the control group.

Fasting blood glucose (FBG), lipid profile, and fasting serum insulin (which was measured using an ELISA kit, Sandwich principle). Levels were assessed both at baseline and following either celecoxib or diclofenac therapy.

Using the quantitative insulin sensitivity check index (QUICKI) formula from fasting plasma glucose and fasting plasma insulin, insulin sensitivity was ascertained:

QUICKI = 1/ (log [FPI in μU/l] + log [FPG in mg/dl]).

Blood samples were taken at baseline and at the conclusion of the six-week treatment period. Insulin and fasting glucose were measured, and the QUICKI index was computed to evaluate variations in insulin sensitivity.

Statistical analysis

The findings were presented as percent changes or mean ± standard error of the mean (SEM). ANOVA and the student t-test were used to determine the degree of significance of the statistical analysis, which was carried out using the Microsoft Excel program. A p-value of less than 0.05 was considered significant.

Ethical consideration

The study was carried out at the National Diabetes Center/ Mustansiriyah University, and the center's ethics committee gave ethical approval. Before participating in the study, all participants gave informed consent for inclusion. This study was conducted in accordance with the Declaration of Helsinki, and an ethics committee in the National Diabetes Center approved the protocol.

RESULTS

Baseline Characteristics

In this study, we summarize the clinical and demographic characteristics of study participants and compare patients with type 2 diabetes to control subjects (Table 1).

Table 1. Demographic Variables, Clinical Parameters, and Metabolic Characteristics of Type 2 Diabetes Patients and Control objects

Variables	Patients with Type 2 diabetes	Control subjects
Number	136 (100%)	64 (100%)
Gender (male/female)	44 (32%) male/92 (68%) female	28 (43%) male/36 (57%) female
Age (years)	40-55	40-57
Duration of diabetes(years)	3-6	nil
Fasting plasma glucose	92-293.4	81-99.9
Total cholesterol≥296 mg/dl	72	nil
Triglycerides≥114.66	48	nil
Treatment with glibenclamide	72 (53%)	nil
Treatment with metformin	24 (18%)	nil
Treatment with (glibenclamide+ metformin)	40 (29%)	nil

We present data on insulin sensitivity and related metabolic parameters in various groups of participants, comparing controls, hyperlipidemic diabetics, and normolipidemic diabetics before and after treatment with diclofenac and celecoxib. Statistical significance is denoted by *p ≤ 0.05 in comparison to the control group. Additionally, non-identical superscripts (a, b) within the same drug-treated group suggest a significant difference, p ≤ 0.05. The data are shown as mean values with standard error of the mean (SEM) (see Table 2).

The table's findings showed that both normolipidemic and hyperlipidemic diabetics had significantly higher fasting plasma glucose levels than the controls (p≤0.05). When comparing hyperlipidemic and normolipidemic diabetics to controls, baseline plasma insulin levels were either significantly higher (p≤0.05) or not significantly different (p≥0.05). Nonetheless, QUICKI scores were considerably lower in diabetics with hyperlipidemia and normolipidemic than in controls.

Table 2. Comparative Tests of Celecoxib and Diclofenac on Insulin Sensitivity Parameters and Glycemic in Normocholesterolemic and Hyperlipidemic Objects

Groups	Type of Therapy	Duration of therapy	FPG (mg/ml)	Fasting insulin level (µiu/ml)	QUICKI (µiu/ml+mg/dl)
Controls N=48	Without treatment	Nil	89.28±0.10	8.23±1.09	0.360±0.008
Hyperlipidemic N=30	Diclofenac N=21	Baseline	211.5±2.57*[a]	11.4±0.78*[a]	0.300±0.008*[a]
		After 8 weeks	179.1±1.74*[b]	13.78±0.83*[b]	0.300±0.007*[a]
	Celecoxib N=39	Baseline	178.92±0.73*[a]	9.61±1.24[a]	0.320±0.007*[a]
		After 8 weeks	158.±0.53*[b]	12.38±1.12*[b]	0.310±0.005*[b]
Normal cholesterol and N=42	Diclofenac N=21	Baseline	174.42±1.02*[a]	12.35±0.96*[a]	0.300±0.005*[a]
		After 8 weeks	131.04±0.78*[b]	15.00±0.83*[b]	0.305±0.004*[a]
	Celecoxib N=21	Baseline	124.02±0.35*[a]	10.71±1.46[a]	0.324±0.005*[a]
		After 8 weeks	121.32±0.29*[a]	13.43±1.36*[b]	0.314±0.005*[b]

Notes: Data are presented as mean ±SEM
N= number of subjects
** Significant difference P≤0.05*
Non-identical superscription (a, b) within the same drug treatment group represents a significant difference p<0.05

When compared to baseline values, hyperlipidemic diabetics treated with diclofenac demonstrated a significant increase in serum insulin levels (% changes +23.720), along with a considerable decrease in FPG (% changes were -15.38) and a non-significant difference (p≥0.05) in QUICKI values (% changes -1.32). Meanwhile, treatment with celecoxib produced a significant decrease (p≤0.05) in serum fasting glucose and QUICKI values (% changes were -11.71, -2.84 respectively), along with a considerable elevation (p≤0.05) in serum insulin levels (% changes + 28.81) in comparison to baseline values.

When diclofenac was administered to diabetics with normolipidemic, there was a significant decrease (p≤0.05) in fasting serum glucose levels (% changes -24.88) and a significant increase (p≤0.05) in serum insulin levels (% changes +21.39) with non-significant changes (p≥0.05) in QUICKI values (% changes + 0.99) in comparison to baseline values. Conversely, when celecoxib was administered, there was a significant increase (p≤0.05) in serum insulin levels (% changes + 25.34) and a significant decrease (p≤0.05) in QUICKI values (% changes -3.09) with non-significant alteration (p≥0.05) in fasting serum glucose levels (alterations – 2.26) in comparison to baseline values.

About how these medications affected insulin sensitivity, diclofenac did not significantly change insulin sensitivity in diabetics who were hyper- or normolipidemic, while celecoxib significantly decreased insulin sensitivity. Due to celecoxib's high level of selectivity as a COX-2 inhibitor, it may have a stronger inhibitory effect on pancreatic COX-2-derived PGE2, which could account for some of the variation in the two medications' effects on insulin sensitivity.

DISCUSSION

Both hyper- and normolipidemic diabetic patients had significantly higher fasting serum glucose levels and fasting insulin levels than the control group. Meanwhile, the insulin sensitivity measured by the QUICKI was significantly lower in the diabetic patients than in the control group [12].

Individuals diagnosed with type 2 diabetes exhibit elevated serum insulin levels, which are expected to be further elevated by their elevated blood glucose levels. In those patients, the pancreatic β cells are normal, but the amount of insulin secreted is inadequate to counteract the insulin resistance [13]. Therefore, Insulin resistance is frequently observed in individuals suffering from type 2 diabetes mellitus. This can be defended as lowering the effectiveness of insulin in reducing blood glucose by directly promoting glucose uptake into muscles and fat cells as well as by increasing hepatic glucose storage and reducing hepatic glucose production [14].

This research demonstrated that treating hyper- and normolipidemic diabetic patients for eight weeks with diclofenac 100 mg/day led to a significant decrease in fasting serum insulin levels and a significant increase in

FPG. However, there was no significant change in insulin sensitivity measured by QUICKI when compared to baseline values. Conversely, treating hyperlipidemic patients with celecoxib 200 mg/day resulted in a significant decrease in fasting serum insulin levels and QUICKI, as well as a significant increase in fasting serum insulin levels [15].

Celecoxib, on the other hand, significantly increased serum levels and decreased QUICKI in normolipidemic patients without significantly changing FPG levels. In both hyper- and normolipidemic diabetics, both medications significantly raised serum insulin levels [1, 16]. This effect may have been partially attributed to the drug's mechanism of action, which involves inhibiting Cox2. Given that cox2 is predominantly expressed in the pancreatic islet in both stimulated and unstimulated conditions, the high basal levels of nuclear factor NF_IL6 in the islet may be connected to this unique circumstance. Under physiological conditions, the islet synthesizes PGE2, a process known to be stimulated by glucose because cox2 predominates in the islet [17].

PGE2 is known to be an inhibitor of glucose-induced insulin secretion in B-cells, which leads to its involvement as a regulator of glucose homeostasis. Therefore, medications that block PGE2 derived from COX2, such as COX2 selective inhibitors, may be able to improve abnormal insulin secretion in diabetic human subjects [18].

Comparing diclofenac, a relatively selective cox2 inhibitor, to celecoxib, which increases insulin resistance by reducing insulin sensitivity. This was seen in this patient group, where the percentage change in fasting serum insulin levels was greater in the celecoxib-treated group than in the diclofenac-treated patients. However, a different study found that giving obese or overweight non-diabetic subjects 200 mg of celecoxib daily for four weeks significantly increased their insulin sensitivity. This suggests that insulin resistance may also be caused by aging, medications, obesity, and exercise [19].

The results imply that COX-2 inhibition can increase insulin sensitivity in T2DM patients; however, the impact may vary depending on the patient's lipid profile and the degree of COX-2 selectivity. Celecoxib—a highly selective COX-2 inhibitor—showed more of an impact on hyperlipidemic patients compared to diclofenac. This could be because of its more potent anti-inflammatory properties, which may lessen the pro-inflammatory condition linked to hyperlipidemia [20].

Elevated insulin levels may signal better glycemic control but could also indicate insulin resistance. Celecoxib, in particular, appears to benefit individuals with hyperlipidemia by reducing inflammation – a known contributor to insulin resistance – potentially improving insulin sensitivity and glucose management. Further research to elucidate this relationship is essential for developing targeted diabetes treatment strategies [21, 22].

Celecoxib and diclofenac both increased insulin sensitivity in patients with normal cholesterol levels, suggesting that inflammation may contribute to insulin resistance even in the absence of dyslipidemia. On the other hand, compared to patients with hyperlipidemia receiving celecoxib, the improvement was less pronounced [23, 24].

Particularly in patients with hyperlipidemia, where highly selective inhibitors like celecoxib may offer additional benefits for improving insulin sensitivity, the use of COX-2 inhibitors in T2DM patients may need to be customized. Particularly in patients with hyperlipidemia, where highly selective inhibitors like celecoxib may offer additional benefits for improving insulin sensitivity, the use of COX-2 inhibitors in T2DM patients may need to be customized [25, 26]. Chronic inflammation has been associated with insulin resistance, suggesting that addressing this inflammation may be beneficial for metabolic health, and the body is attempting to maintain glucose homeostasis. The study emphasizes the potential role of COX-2 inhibitors in reducing inflammation, which could offer a dual advantage For patients with hyperlipidemia [27].

CONCLUSIONS

This study shows that patients with type 2 diabetes, especially those with hyperlipidemia, may have improved insulin sensitivity when COX-2 inhibition is used, especially with highly selective inhibitors like celecoxib. More studies with bigger sample sizes and longer treatment times are required to validate these results and investigate the underlying mechanisms.

AUTHOR CONTRIBUTIONS

Safaa Ehssan Atta and Baydaa Ahmed Abed did preliminary data analysis, and Isam Noori Salman wrote the article. All other authors collaborated to review the article. All authors read and approved the final manuscript for publishing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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