

# Study of Combination of Metformin and Pregabalin on HbA1c and DASS21 in Diabetic Patients Suffering from Anxiety

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## ABSTRACT –

People diagnosed with DM are approximately 20% more likely to suffer from anxiety than those without diabetes. Metformin is the first line therapy for treating T2DM, whereas pregabalin is the first line therapy for treating diabetic neuropathy as well as generalized anxiety disorder (GAD). The objective of this study was to investigate the effect of combining pregabalin with metformin in patients who suffer from anxiety and see to what extent does it reduce anxiety symptoms as well as their glycated hemoglobin level. Related data were collected from T2DM individuals that were undergoing treatment with metformin alone and those with metformin and pregabalin combination. A greater decrement in anxiety symptoms and HbA1c occurred in patients taking the combination therapy. Besides pregabalin's use to decrease neuropathy symptoms it can also alleviate anxiety symptoms in diabetic patients bringing about a better glycemic control in them.

*Key words: Type 1 diabetes, Type 2 diabetes, Metformin, pregabalin.*

## I. INTRODUCTION

Diabetes mellitus (DM) is becoming more common at an alarming rate. What was once thought to be a minor ailment affecting the elderly is now a major cause of morbidity and mortality among the young and middle-aged [1]. In recent years, the most noteworthy change in the DM pattern has been a movement in the age of onset to a younger age [2]. The reasons for the escalating including population ageing, economic development, urbanization, life style and sedentary lifestyles lack of physical activity [3]. Despite the advances in DM treatments yet it still continues to progress in bad terms. Metformin remains one of the most popular oral glucose-lowering medications, widely regarded as first line therapy for patients with T2DM [4]. T2DM and its consequences have made a significant contribution to the global burden of death and disability. Half of patients with T2DM followed by microvascular complications coronary artery disease (CAD), peripheral arterial dis-

ease, and stroke) and 27% with macrovascular complications (diabetic nephropathy, neuropathy, and retinopathy) [5]. Diabetic neuropathies are the most widespread chronic complications of DM affecting different parts of the nervous system and possessing diverse clinical outcomes [6]. The risk of developing diabetic neuropathy related to both the magnitude and duration of hyperglycemia, in addition to that, some patients possess a genetic attribute that predispose them to developing such complication.

Generally, in terms of pharmacology, it has been approved duloxetine and pregabalin for the treatment of diabetic neuropathic pain [7]. Pregabalin has been applied for the treatment peripheral and central neuropathic pain, generalized anxiety disorder, and as adjunctive therapy for partial seizures [8]. In patient with T2D, anxiety has long been linked to poor metabolic outcomes and increased medical complications [9]. according to the study, Patients with T2D have a 60 percent higher frequency of depression or anxiety disorders than the general population [10]. In T2D, lifetime depression and anxiety raise the risk of severe psychological symptoms, hyperglycemia, and health-behavioral issues [11]. Study revealed that diabetes causes some changes in the body especially in brain, such as cerebral atrophy and lacunar infarcts, as well as hypoperfusion and hyperperfusion [12]. However, patients with T1D and T2D directly reduced in brain sizes and localized to the hippocampus, as well as an inverse connection between glycemic management and hippocampal volume. However, the only significant predictor of hippocampus volume was HbA1C [12]. It has been revealed that depression related to neurodegenerative, especially in the prefrontal cortex and hippocampus [13]. According to above study, I tried to investigate the combination between metformin and pregabalin on HbA1c and DASS21 scores.

## II. MATERIALS AND METHODS

### A. Patients

This study was carried out in outpatients' department at Layla Qasm Hospital in Hawler City during the period from December 2019 to May 2020. This study included 52 diabetic patients on metformin monotherapy and 64 diabetic patients on combination of metformin and pregabalin.

### B. Patients Group 1

T2DM patients receiving metformin (30 males, 22 female) were with averaged mean of age  $40 \pm 10$  years.

### C. Patients Group 2

T2DM patients receiving metformin and pregabalin (44 males, 20 female) were with averaged mean of age  $40 \pm 10$  years.

### D. Drugs used in the current study

Drug used in present study was (Metformin 500mg and Pregabalin 150 mg).

### E. Diagnostic kits and chemicals

Diagnostic kit with their supplier was Commercial kit for measurement of HbA1c COBAS INTEGRA/COBAS c, Germany

### F. Instruments

Instruments with their suppliers was HbA1c Lab medical appliance (Cobas Roche – Germany).

## III. METHODS AND SAMPLING

### A - Sampling and measurement of HbA1c

Three ml of blood collected from the patient and control under sterile condition by using sterile syringe. The blood is transferred to a disposable tube without anti-coagulant and the serum obtained by centrifugation for 5 minutes at 50rpm and then put the sample of COBAS after calibration of it, it gives the result.

### B - Sampling and Measurement of DASS21

Depression Anxiety Stress Scale 21 (DASS21) was translated into Kurdish and the patients were asked by an official trainee and have their answers measures and recorded twice within the period of three months.

## IV. STATISTICAL ANALYSIS

All values are expressed as mean  $\pm$  standard error of the mean. Data are entered into computer sys-

tem using GraphPad Prism 8 software for all mathematics and statistical analysis. The means and standard errors were calculated for different variables, including age, DASS21, HbA1c. The student's t test is used to determine the significant difference in means of each two groups.  $p \leq 0.05$  was considered to be the lowest limit of significance.

## V. RESULTS AND DISCUSSION

### A- Glycated Hemoglobin (HbA1c)

Table 4.1 shows the mean  $\pm$ SE values of HbA1c in group 1 and group 2. An independent t-test was conducted to compare HbA1c levels in group 1 and group 2. There was a significant decrement in the HbA1c levels for group 1 pretreatment ( $7.325 \pm 0.531$ ) vs. post-treatment ( $6.650 \pm 0.536$ ),  $p=0.0042$  and group 2 pretreatment ( $7.650 \pm 0.492$ ) vs. post-treatment ( $6.750 \pm 0.357$ ),  $p=0.0088$ .

Table 4.1 Comparison of HbA1c between group 1 and group 2 after three months of treatment.

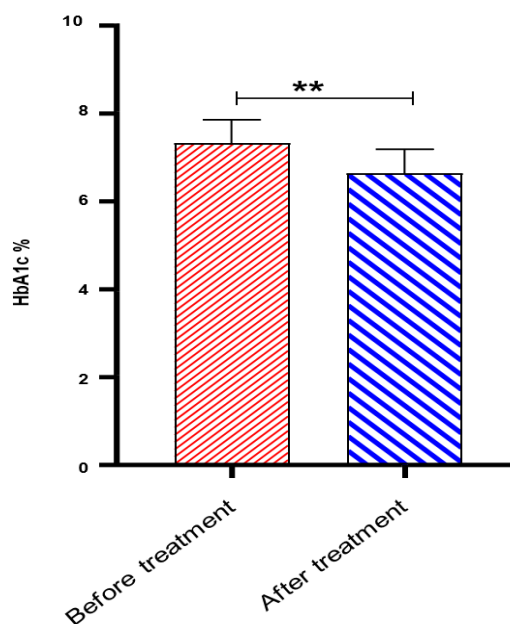
Variable	Group, Mean (SE)	
	Group 1 (n = 52)	Group 2(n= 64)
HbA1c	6.650(0.536)	6.750(0.357)
<i>p</i> value*	0.004	0.008

Values are represented as mean  $\pm$  standard error

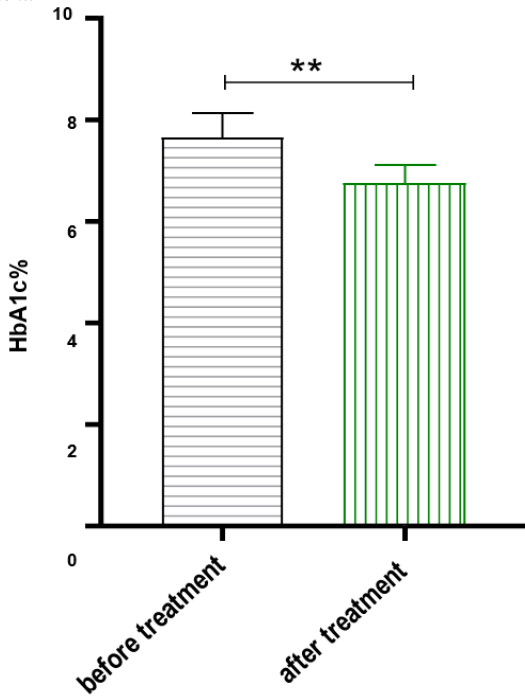
\**p* value is significant at  $< 0.05$

Group 1 (treated with metformin)

Group 2 (treated with metformin and pregabalin)



**Figure 4.1:** Barcharts demonstrating the effect of metformin on HbA1c level in T2DM patients, before and after 3 months of treatment.



**Figure 4.2:** Barcharts demonstrating the effect of the combination metformin and pregabalin on HbA1c level in T2DM patients, before and after 3 months of treatment.

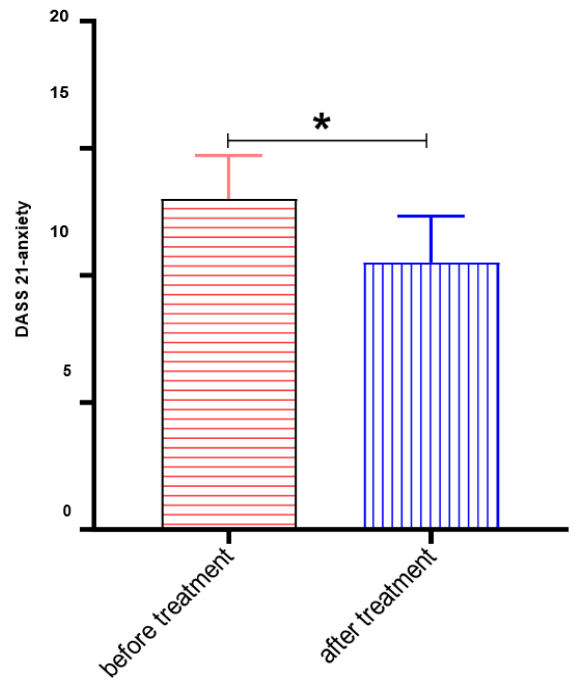
DASS21 – anxiety Score

Table 4.2 shows the mean ±SE values of DASS21 Anxiety score in group 1 and group 2. An independent t-test was conducted to compare the anxiety level obtained from DASS21 in group 1 and group 2. There was a significant decrement in the level of anxiety for group 1 pre-treatment (13.0±1.73) vs. post-treatment (10.5±1.84), p value≤0.0305 and group 2 pre-treatment (14.75±1.49) vs. post-treatment (8.75±0.85), p value≤ 0.034.

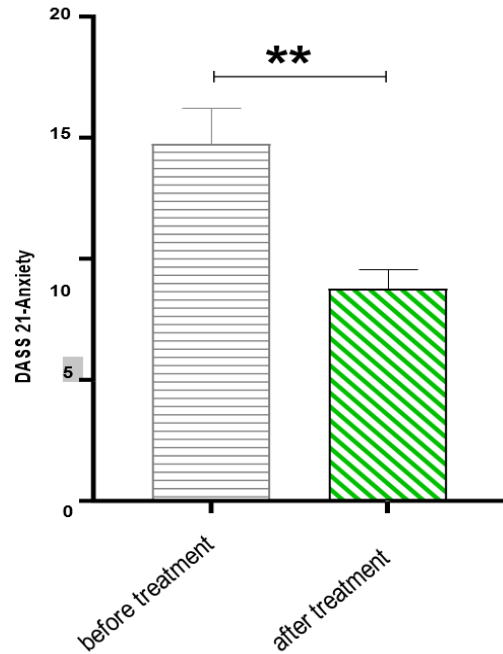
**Table 4.2:** Comparison of DASS21-Anxiety between group 1 and group 2 after three months of treatment.

Variable	Group, Mean (SE)	
	Group 1 (n = 52)	Group 2(n = 64)
DASS21- Anxiety	10.50(1.848)	8.750(0.853)
<i>p</i> value*	0.030	0.034

Values are represented as mean ± standard error  
 \**p* value is significant at < 0.05  
 Group 1 (treated with metformin)  
 Group 2 (treated with metformin plus pregabalin)



**Figure 4.3:** Barcharts demonstrating the effect of metformin on level of anxiety in T2DM patients, before and after 3 months of treatment.



**Figure 4.4:** Barcharts demonstrating the effect of metformin and pregof abalin on level of anxiety in T2DM patients, before and after 3 months treatment.

T2D is characterized by insulin resistance and, related with deficiency of insulin secretion. However,

with time there is progressive  $\beta$ -cell failure and worsening insulin deficiency continues [14]. Patients with T2D lead to risk of developing complications, which include microvascular complications manifesting as diabetic nephropathy, neuropathy, and retinopathy as well as macrovascular complications (MVC) manifesting as CAD, PAD, and stroke. Pregabalin considered as first line therapy for treating diabetic neuropathy does not only alleviate symptoms of nephropathy but also acts as anxiolytic [15]. A common pathogenesis exists between anxiety and depression with diabetes giving a feasible link between them. In this study, DASS21 and HbA1c of 8 patients in total were recorded on two occasions separated by three months. A significant reduction in HbA1c scores was recorded in metformin group with ( $p=0.004$ ) as well as with metformin plus pregabalin group with ( $p=0.008$ ), this emphasizes the importance and effectiveness of metformin role in glycemic control. It has been revealed that, metformin accomplishes this effect by reduction intestinal glucose absorption, induced peripheral glucose uptake, lowering fasting plasma insulin levels and increasing insulin sensitivity, which result in a reduction of blood glucose levels without causing hypoglycemia [4]. Clinical data collection revealed that metformin alone as metformin with pregabalin combination maintained its aim and efficacy. Moreover; Referring to (Figures 4.3 and 4.4), a significant reduction occurred in anxiety score in both groups of patients; metformin only ( $p=0.00305$ ) and metformin plus pregabalin ( $p=0.0034$ ). The significant reduction in anxiety in metformin only group (Figure 4.3) might be due to the Covid19 circumstances where patients did not suffer from anxiety of daily life duties, and had spare time to a great extent to spend with their families and beloved ones and so removing the burden of anxiety. A greater decrement in anxiety in metformin plus pregabalin group (Figure 4.4) is contributed to the anxiolytic effects of pregabalin. Pregabalin not only reduces the excitatory neurotransmitters that cause anxiety but also decreases the expression of pro-inflammatory cytokines which are expressed during neuropathic pain therefore minimizing the pain this also contributed to the reduction of anxiety levels. It has been revealed that untreated anxiety is not only significantly related with hyperglycemia but it also impedes efforts to achieve normoglycemia by interfering with diabetes treatment through activation of sympathetic nervous system or via hypothalamic pituitary adrenal [16]. In general, anxiety can be illustrate as a feeling of anxiety, nervousness or anxiety about an impending circumstance or event with an uncertain outcome which is followed by symptoms avoidance of certain people, physical sensations such as palpitations, dizziness, sweating, physical complaints such as headaches and indigestion [17]. However, there are several clinically im-

portant subtypes of anxiety disorders; the most common in primary health care is generalized anxiety disorder (GAD) [18]. However, study on Rates of GAD revealed that phobias considerably higher in diabetic patient when compared to community samples [18]. Other mental conditions are equally common in people with diabetes, the frequency of depression is 2:58 times higher in people with diabetes, in most cases remain undetected. However, anxiety has not been extensively studied in the context of medical illness, which may be because anxiety has been overshadowed by the depression debate or dismissed as a latent pathological process. On the other hand, pregabalin is an effective treatment for the prevention of relapse in patients with GAD. Other beneficial therapies exist achieving efficacy in treating anxiety. Cognitive behavioral therapy (CPT) has been studied and considered to be effective in treating anxiety and depression [18].

## CONCLUSION

The present study demonstrated a significant decrement in HbA1c in patients treated with metformin alone ( $p=0.042$ ) and combination of metformin and pregabalin ( $p=0.0088$ ). In addition to that, despite the fact patients on metformin only showed a significant reduction in anxiety level ( $p=0.0305$ ), but patients on metformin plus pregabalin showed an even greater reduction anxiety levels ( $p=0.0034$ ). Anxiety disorders are prevalent, disabling, and often untreated in primary care and may worsen co-existing diseases.

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