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REVIEW ARTICLE

Correlation of Norepinephrine with some biochemical Parametric in Patients with type 2 diabetes mellitus.

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Abstract

Background: Type 2 diabetes is a chronic metabolic disorder characterized by high blood sugar levels (hyperglycemia) resulting from the body's reduced ability to produce or use insulin effectively. Insulin is a hormone that regulates blood sugar levels, and in type 2 diabetes, the body either does not produce enough insulin or becomes resistant to its effects. This causes a buildup of glucose in the bloodstream, which can eventually harm organs and tissues. This study was carried out on patients who attended the Diabetes and Endocrinology Specialist Center of Marjan City for Medical Education in Babil Province., all patients were diagnosed by a specialist physician. The practical side of the study was performed at the Clinical Chemistry Laboratory in the College of Medicine and College of Biotechnology, Al-Qadisiyah University.

Objectives: Investigate the Correlation of Norepinephrine with some biochemical Parametric in patients with type 2 diabetes mellitus.

Methods: The method used in this study Enzyme-Linked Immunosorbent Assay (ELISA).

Results: In the metformin treatment group and the group not using antidiabetic treatment, there are weak associations between norepinephrine and insulin levels, but these associations are not statistically significant. In the diamicron MR treatment group, norepinephrine is significantly correlated with lower levels of fasting blood glucose and HbA1c.

Conclusions: Norepinephrine dysregulation may be associated with type 2 diabetes, regardless of specific treatments, indicating a potential role of norepinephrine in the pathophysiology of the disease.

Keywords: Norepinephrine (NE); Type 2 diabetes mellitus (T2DM); Insulin Resistance (IR)

Introduction:

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia, which results from a combination of insulin resistance and relative insulin deficiency(1). T2DM accounts for more than 90% of all diabetes cases worldwide and is a major global health concern due to its increasing prevalence, high morbidity and mortality rates, and economic burden(2). The prevalence of T2DM is strongly associated with several risk factors such as age, obesity, physical inactivity, poor diet, family history of diabetes, and certain genetic and environmental factors(3). The pathophysiology of T2DM is complex and involves multiple pathways, including impaired insulin secretion, increased hepatic glucose production, and decreased glucose uptake in peripheral tissues such as skeletal muscle and adipose tissue(4). T2DM can lead to a range of complications such as cardiovascular disease, nephropathy, neuropathy, retinopathy, and foot ulcers, among others. These complications can result in significant morbidity and mortality, decreased quality of life, and increased healthcare costs(5). T2DM is managed with a combination of lifestyle changes, such as diet and exercise, and pharmaceutical therapy targeted at improving glycemic control and lowering the risk of complications(6). There are several classes of medications available for the management of T2DM, including metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter-2 inhibitors, among others(7). The choice of medication depends on various factors, including the patient's glycemic control, comorbidities, and individual preferences. Norepinephrine, also known as noradrenaline, is a hormone and neurotransmitter that plays a role in the sympathetic nervous system's "fight or flight" response(8). It is released by nerve fibers in response

to stress or other stimuli and acts on various organs and tissues throughout the body(9). In the context of type 2 diabetes mellitus (T2DM), norepinephrine can have several effects: Norepinephrine can increase blood glucose levels by stimulating the breakdown of glycogen (the storage form of glucose) in the liver(10). It does this by activating enzymes involved in glycogenolysis, the process of glycogen breakdown. This effect can be problematic for individuals with T2DM, as they already have impaired insulin function and elevated blood glucose levels(11). Norepinephrine has been implicated in the development of insulin resistance. Chronic elevation of norepinephrine levels can impair insulin signaling and reduce insulin sensitivity in target tissues such as muscle and adipose tissue. This can contribute to the pathophysiology of T2DM, where insulin resistance is a key feature(12). Norepinephrine stimulates the breakdown of stored fats (lipolysis) in adipose tissue. This releases free fatty acids into the bloodstream, which can further contribute to insulin resistance and increase the risk of cardiovascular complications associated with T2DM(13).

The Materials and Methods

The Subjects

Subjects in this case-control study were patients with type 2 diabetes between the ages of 35-80 years who have high insulin resistance. The study was conducted between the 1st of September 2022, until the 1st of April 2023. The total number of participants initially selected was 140. However, 20 participants were excluded due to being overweight and not fasting for 12 hours. Therefore, the final sample consisted of 120 participants, with each group consisting of 15 men and 15 women. The participants were distributed into four groups (Metformin Treatment group, Diamicron MR Treatment group, Without treatment group, and Control group). It is worth noting that the selection of healthy individuals was similar to the diseased cases in terms of age, sex, body mass index, socio-economic status, and other related conditions.

The Blood Sample Collecting

The obtain a sample of venous blood, a tourniquet was applied to the subject's arm and 3 ml of blood was collected. The blood was transferred to a gel tube for serum separation. The blood was allowed to coagulate for 30 minutes before being centrifuged for 10 minutes at 3000 rpm. The serum was collected in four repeaters in a sterile Eppendorf tube and stored at -20 ⍰.

The Detection of Norepinephrine concentration

The principal measure of the levels of Norepinephrine in the ELISA kit is the Competitive-ELISA method. In this method, the analyte of interest in this case Norepinephrine competes with a labeled form of the same analyte for binding to a limited amount of antibodies coated onto the wells of the ELISA plate. The concentration of the analyte in the sample is inversely proportional to the amount of labeled analyte detected, as the labeled analyte is displaced by the unlabeled analyte in the sample. It was that the proper steps of the work method were followed, and the reagents were prepared according to the instructions of the supplying company. Following the correct procedure and using properly prepared reagents is crucial for obtaining reliable results in ELISA assays.

The Detection of Insulin concentration

The Sandwich-ELISA method is used to measure insulin levels; the micro ELISA plate is pre-coated with an antibody specific to the protein of interest, in this case, human insulin. The protein-containing sample is added to the plate, and if the protein is present, it will attach to the pre-coated antibody. The plate is then treated with a second antibody that is also specific to the protein of interest and binds to a different location on the protein. In most cases, the second antibody is conjugated to an enzyme, such as horseradish peroxidase, which generates a detectable signal in the presence of a substrate. Finally, a substrate is introduced to the plate, and the enzymatic reaction mediated by the attached enzyme results in the formation of a product.

The Detection of FBG concentration

The Principle (Trinder Method for Glucose): this is a commonly used method for the quantitative determination of glucose in biological samples. It involves the use of two enzymes, glucose oxidase (GOD) and peroxidase (POD), to catalyze the oxidation of glucose to gluconic acid and hydrogen peroxide. The hydrogen peroxide, in the presence of POD, reacts with chloro-4-phenol and p-aminophenazone (PAP) to form a red quinone imine. The intensity of the resulting color is proportional to the concentration of glucose in the sample and can be measured spectrophotometrically at 500 nm. (188).

The Reaction can be Summarized as Follows:

Glucose + GOD → Gluconic acid + H2O2

H2O2 + POD + chloro-4-phenol + PAP → Quinone imine + H2O

The Trinder method is sensitive and specific for glucose and is commonly used in clinical laboratories for the diagnosis and monitoring of diabetes mellitus.

The Detection of Blood HbA1c (Automated HbA1c Assay)

The boronate affinity assay serves as the foundation for the AfinionTM HbA1c test. A boronic acid conjugate is used in this assay to bind to the cis-diols of glycated hemoglobin (HbA1c) in a blood sample. The test cartridge contains all of the chemicals required to measure the percentage of HbA1c, including the boronic acid conjugate. The blood sample is collected by the integrated sampling equipment, which is automatically diluted and blended with a solution that releases hemoglobin from the erythrocytes. After the glycated hemoglobin precipitates, the boronic acid conjugate bonds to it. The mixture is then passed over a filter membrane, and any excess conjugate is washed away using a washing reagent. The precipitate on the membrane is evaluated by measuring the reflectance of the blue (glycated hemoglobin) and red (total hemoglobin) color intensities. The ratio between them is proportional to the sample's HbA1c level.

The Statistical Analysis

A descriptive statistical analysis was employed in this study, which includes summarizing and describing the data using measures like mean, median, mode, and standard deviation. Data from all participants were input and analyzed with suitable statistical tests using the statistical package for social sciences (SPSS) software for Windows, version 23, IBM, US,16. Descriptive statistics were reported in the form of mean and standard deviation (SD) for continuous variables and frequencies and proportions (No. and%) for categorical variables. The variance analysis The one-way ANOVA test was performed to compare the means of variables for four groups, and the Tukey HSD test was employed to calculate the difference between these totals.

Results

The Biochemical Markers

As indicated in Table 1, the (mean ± SD) of Ages and Genders among G1, G2, and G2 with G4 is not significant at (P. value >0.05). The (mean ± SD) of BMI, Norepinephrine, Insulin, Fasting Plasma Glucose, and Hemoglobin A1c among G1, G2, and G2 with G4 is statistically significant at (P. value ≤ 0.05).

The Correlation Norepinephrine

Table 2 presents the correlation results between norepinephrine and the variables (insulin, FBG, and HbA1c) in different treatment groups:

In the metformin treatment group, Norepinephrine and insulin have a mild negative connection (r = -0.053, p = 0.782), indicating that higher norepinephrine levels are associated with somewhat lower insulin levels. This association, however, is not statistically significant. Similarly, norepinephrine has no significant relationship with FBG (r = -0.019, p = 0.919) or HbA1c (r = -0.053, p = 0.775).

In the diamicron MR treatment group, Norepinephrine and insulin have a weak positive connection (r = 0.037, p = 0.845), showing that higher norepinephrine levels are related with slightly higher insulin levels. This association, however, is not statistically significant. Norepinephrine, on the other hand, has a substantial negative connection with FBG (r = -0.463*, p = 0.010) and HbA1c (r = -0.387*, p = 0.034). This implies that in the diamicron MR therapy group, increased norepinephrine levels are related with reduced FBG and HbA1c levels.

In the group not using antidiabetic treatment, Norepinephrine and insulin have a weak negative connection (r = -0.168, p = 0.374), showing that higher norepinephrine levels are associated with somewhat lower insulin levels. This association, however, is not statistically significant. Similarly, there is no significant relationship between norepinephrine and FBG (r = -0.033, p = 0.865). However, there is a significant negative relationship between norepinephrine and HbA1c (r = -0.389*, p = 0.033), meaning that higher norepinephrine levels in the non-diabetic group are associated with lower HbA1c levels.

Discussions

In this study, we note that BMI increases in patients who use Dianicron MR treatment side effects of this treatment are weight gain, increase appetite and decrease physical activity levels, which can contribute to a higher BMI in diabetic patients who use the medication (14). Gliclazide stimulates the pancreas to release more insulin, which helps to lower blood sugar levels (15). Insulin, on the other hand, encourages the storage of glucose as fat in adipose tissue, which might result in weight gain (16). Found a difference in body mass index between the control group and the group of patients using metformin treatment, metformin treatment leads to side effects in the gastrointestinal such as nausea, diarrhea, and loss of appetite, which can contribute to weight loss and a lower BMI in some patients (17).

The result of the study suggests that norepinephrine concentration is elevated in patients with type 2 diabetes, regardless of treatment, compared to the control group. The reason for the elevated norepinephrine concentration in patients with type 2 diabetes may be related to the physiological effects of the disease. The sympathetic nervous system (SNS) is a part of the autonomic nervous system that regulates the body's response to stress, exercise, and other physiological challenges(18). In people with type 2 diabetes, there is evidence of chronic activation of the SNS, which may lead to elevated norepinephrine levels(19). A study has shown that patients with type 2 diabetes have increased sympathetic nervous system activity, which is associated with insulin resistance(20). Sympathetic nervous system activation leads to increased release of norepinephrine from nerve endings and adrenal glands, which can contribute to elevated norepinephrine levels in the blood(19).

The difference in insulin concentration between the groups receiving metformin and Diamicron MR therapy is also noteworthy, as the group receiving Diamicron MR therapy showed a slightly higher increase in insulin concentration compared to the group receiving metformin therapy (21). This could suggest that Diamicron MR may be a more effective treatment for increasing insulin concentration in individuals with diabetes compared to metformin therapy. Diamicron MR stimulates insulin secretion from the pancreas, which results in an increase in insulin concentration (22). Metformin, on the other hand, acts largely by decreasing glucose synthesis in the liver, resulting in a fall in blood glucose levels and, as a result, a decrease in insulin secretion (23). It is also important to note that individual responses to medication can vary, and other factors such as differences in dosages, treatment duration, and patient characteristics could also contribute to the observed difference in insulin concentration between the two groups. The reason for this increase in insulin concentration in the untreated group compared to the control group could be due to several factors. One of the most likely explanations is insulin resistance(IR). IR is a condition in which the cells of the body become less sensitive to insulin, resulting in increased insulin secretion to compensate for insulin's decreased efficiency. This can eventually lead to hyperinsulinemia, or an elevated concentration of insulin in the blood (24). Other factors that could contribute to the increase in insulin concentration in the untreated group include lifestyle factors such as a high-carbohydrate diet, physical inactivity, and obesity (25). These factors can also contribute to insulin resistance and increased insulin secretion.

The reason for the differences in Fasting Blood Glucose concentration between the groups may be due to the different mechanisms of action of the medications and the varying levels of glycaemic control achieved(26). Metformin is frequently used as first-line therapy for type 2 diabetes due to its ability to reduce blood glucose levels without inducing weight gain or hypoglycemia (27). The metformin group had a lower increase in Fasting Blood Glucose concentration than the other groups, which could be attributed to its capacity to effectively reduce hepatic glucose synthesis and improve insulin sensitivity (28). Diamicron MR is often used as a second-line therapy for type 2 diabetes when metformin alone is not sufficient to control blood glucose levels (29). The slightly higher increase in Fasting Blood Glucose concentration in the Diamicron MR group compared to the metformin group may be due to its mechanism of action, which is less effective at reducing hepatic glucose production and improving insulin sensitivity. The group without treatment had the highest increase in Fasting Blood Glucose concentration compared to the control group, which is expected since they did not receive any medication to help manage their blood glucose levels.

The reason for the differences in HbA1c levels between the different groups of patients with diabetes is likely due to sever-

al factors, including variations in the effectiveness of different treatments in controlling blood glucose levels (30), differences in adherence to treatment regimens, and variations in individual patient factors such as age, duration of diabetes, and co-existing medical conditions (31). Patients without using any treatment for their diabetes likely had uncontrolled blood glucose levels, which could have contributed to the highest increase in HbA1c. It's important to note that HbA1c is a long-term measure of blood glucose control and is affected by the average blood glucose level over the previous 2-3 months (32). Therefore, it's possible that some patients may have had fluctuating blood glucose levels during the study period, which could have affected their HbA1c levels.

The Conclusions

The concentration of norepinephrine does not differ between patients with type 2 diabetes who use or do not use metformin or Diamicron MR treatment. However, compared to the healthy group, there is an increase in norepinephrine concentration.

The Table

Table 1: The Demographic Characteristics and Biochemical Parameters between G1, G2, and G3 with G4.

Variables	G1(n = 30)	G2(n = 30)	G3(n = 30)	G4(n = 30)	p
Age (years)					
Mean ±SD	58.23±8.931	56.70±9.319	55.73±8.358	57.23±11.029	0.778
Range	42-70	40 – 70	42 - 70	40 - 70	NS
Gender					
Male, *n* (%)	15 (50.0 %)	15 (50.0 %)	15 (50.0 %)	15 (50.0 %)	0.405
Female, *n* (%)	15 (50.0 %)	15 (50.0 %)	15 (50.0 %)	15 (50.0 %)	NS
BMI(kg/m2)					
Mean ±SD	33.673±6.3320	39.393±7.4136	36.487±9.0646	39.777±8.5062	< 0.011 O**
Range	23.1 – 51.8	26.9 – 55.8	24.3 – 55.8	28.4 – 54.9	
Norepinephrine (ng/mL)					
Mean ±SD	10.12±2.290	10.54±1.468	10.53±1.421	9.0±2.081	< 0.004 O***
Range	1.6 – 12.3	6.4 – 1.3	5.1 – 12.1	5.2 – 12.1	
Insulin (µlU/ml)					
Mean ±SD	15.487±4.6311	16.227±4.7536	20.900±3.4664	3.853±0.4531	< 0.002 O***
Range	8.2 – 24.1	8.2 – 24.2	10.5 – 24.9	3.1 – 4.7	
Fasting Plasma Glucose (mg/dl)					
Mean ±SD	148.10±20.578	134.10±29.037	159.03±17.523	81.47±4.345	< 0.002 O***
Range	115 - 199	95 – 219	95 - 185	73 - 91	
Hemoglobin A1c (HbA1c) (%)					
Mean ±SD	7.567±1.6329	8.157±1.5224	8.933±2.0016	4.347±0.4666	< 0. 001 O***
Range	4.8 – 11.2	5.2 – 11.2	5.6 – 14.7	3.3 – 5.2	

G: Group; n: number of cases; SD: standard deviation; BMI: Body Mass Index; O: one way ANOVA; NS: not significant; **: significant at p ≤ ٠,٠١١; ***: significant at ٠,٠٠٢ ≥ p ≤ ٠,٠٠١

Table 2. The correlation results between norepinephrine and the variables insulin, FBG, and HbA1c in different treatment groups

variables	G1 (N=30)		G2 (N=30)		G3 (N=30)	
	r-value	P-value	r-value	P-value	r-value	P-value
IN	- 0.053	0.782	0.037	0.845	- 0.168	0.374
FBG	- 0.019	0.919	- 0.463*	0.010	- 0.033	0.865
HbA1c	- 0.055	0.775	- 0.387*	0.034	- 0.389*	0.033

IN: Insulin; FBG: Fasting Plasma Glucose; HbA١c: Hemoglobin A١c; *: significant at p ≤ ٠,٠٣٤ ,٠,٠١٠ and ٠,٠٣٣

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