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ORIGINAL ARTICLE

Comparison the Impact of the Metformin and Insulin on Different Biochemical Markers in Type II Diabetes Mellitus

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ABSTRACT

T2DM was called a non-insulin dependent type. The cause is either insulin resistance with insulin insufficiency or from defect in insulin secretion combined with insulin resistance. It usually occurs before 40 years old age, but also can occur at less than that age. About 50% of male and 70% of female cases often are obese.

The management of diabetes has been practiced since the Middle Ages with several treatments. The first treatment called metformin is a biguanide drug that is usually used as the first-line oral treatment for T2DM in people of all ages. The second treatment used is insulin therapy (with or without additional medications) that should be started in newly diagnosed T2DM patients with symptoms (catabolic characteristics such as weight loss, ketosis, or signs associated with hyperglycemia such as frequent urination/polydipsia) and/or have a severe increase in blood sugar levels.

Results: In type II diabetic patients who treated with compare of metformin or insulin The results was indicated a significant difference parameters in duration of treatment and blood glucose , as well as , there was a strong positive correlation between ALT and AST in in treated with metformin or insulin.

Conclusions: In type II diabetic patients, metformin or insulin treatments have the same effect on the activities of ALT, AST, SOD, GST and lipid profile , except for the level of glucose depending on the disease severity, study the correlation of ALT and AST activities with some biochemical markers in type 2 diabetic patients treated with metformin and insulin.

Keywords: T2DM , metformin , insulin , (Glutathion S-transferase (GST).

INTRODUCTIONS

Diabetes mellitus is one of the metabolic processes disorders caused via means of either disturbance in the insulin secretion (type 1 Diabetes), action of insulin (type 2 Diabetes) or both. It is by hyperglycemia, disturbance of carbohydrate, fat. Also, hyperglycemia is associated long-term damage and dysfunction(1)(2). About 90–95% of patients with diabetes are of T2DM type. In past this type was called (noninsulin dependent diabetes), or (adult onset diabetes) (3)(4).

T2DM was called a non-insulin dependent type (5). The cause is either insulin resistance with insulin insufficiency or from insulin secretion combined with insulin resistance (6). It usually occurs befor 40 years old age, but also can occur at less than that age (7) . About 50% of male and 70% of female cases often are obese (8). The causes of T2DM are environmental with genetics or may be medical causes. Furthermore, the risk occurs by the interaction of the genetic underline cause with different environmental contacts faced us during each individual's life (9)(10)

An early assessment of the risk patient's fact, the existence or absence of diabetes complications, and an initial review of previous management/s are all required for comprehensive diabetes management (11).

This will allow providers to bring about patients with diabetes or prediabetes supplementary effectively. management diabetes entails a combination of lifestyle changes, pharmaceutical therapy, and regular blood glucose testing (12).

The treatment of all kinds of diabetes is aimed to reduce the symptoms and avoiding the short and long term technical hitches but blood sugar level must be measured frequently(13) . To adjust the dose of hypoglycemic drugs and insulin, frequent measurement of blood sugar level are required to avoid hypoglycemia occurrence which is lethal (14). When strict dieting is failed in obese and overweight patients, the metformin is the first line for treatment of T2DM(15,16). Metformin is a biguanide that is commonly used as the first-line oral treatment for T2DM in people minor of all ages (17). obstructs by talk into adenosine -activated protein reducing gluconeogenesis progression kinase in the lower liver activating, hepatic Metformin glucose and Metformin monophosphate gluconeogenesis via complicated actions on mitochondrial absorption enzymes (18)(19). Metformin is well tolerated and has side effects, as well as a low risk of hypoglycemia and weight gain (12). has been unproven to slow the of T2DM, the of gluconeogenesis, and lower lowering death rates in sensitivity patients by glucose synthesis (complications) and increasing insulin in tissues (20). It receptors enhances weight by increasing tyrosine kinase activity and activating insulin (12). Metformin glucagon may overweight also help reduce Metformin CVDs by lowering plasma lipid levels via insulin a peroxisome who -activated receptor (PPAR)- diabetics mechanism(18)(21). Food intake may be reduced by incretin-like activities mediated by glucagon -like peptide-1 (GLP-1) (22)(23). Metformin may thus result in unimportant loss in proliferator are or chunky (24)(25).

If non-insulin mono therapy, such as metformin highest tolerable, fails to maintain the A1C aim after a second three months uttered drug, such as GLP-1 agonist receptor or insulin, may be added to the regimen(26)(12). Insulin (by means of or deprived of added means) have to be started in newly patients with diagnosed T2DM who are suggestive (catabolic geographies such as loss weight, ketosis, or hyperglycemia-related features such as polyuria polydipsia) have elevated brutally blood glucose levels Hba1c (ten to twelve percent) (12).

insulin When was revealed almost one hundreds ago years, it was the only available drug for the action of diabetes and persisted to be so until the detection of sulfonylureas , biguanide fifty later years (27).

The Patients should be informed about the clinical picture of T2DM and its treatments on a regular and objective basis (28). Many people with T2DM will need insulin at some point during their lives (29). Insulin should not be delayed in patients with T2DM who do not meet their target glycemic targets (30)(31). To guarantee brilliant quality of adherence, promoter workers should insulin as a completely nonjudgmental, compassionate, and nonpunitive manner (12). In patients with T2DM who are starting insulin therapy, monitoring self of blood glucose (described below) correlates to a considerable enhancement in control glycemic (32)(33). To achieve target glycemic objectives and avoid hypoglycemia, each dose titration requires close and intensive care recurrent of the patient (34)(35).

MATERIAL AND METHOD

The study was achieved by collected of 62 T2DM patients as for take metformin or insulin divided two group (32 treated with metformin and 30 treated with insulin), The collection of samples through the period from 15 march 2021until the 15 of July 2021. The biochemical analysis were done hormones and diabetes in a

Al Sadder Teaching Al Najaf al Ashraf Province Hospital, The age of patients ranged between 35-70 years For the patients to be included, the diagnosis of T2DM has to be validated by a specialized physician. The exclusion criteria were included following Type 1 DM, CVD, Type 2 diabetic patients on anti-hyperlipidaemic medications, renal failure, Cancer and Drug dependence such as cortisol. Withdrawn a total of three milliliters of blood from all participants and gathered into two tubes, 2 ml in Anticoagulant-free gel tube, the serum tube was centrifuged for about 10 minutes at 2000 xg. The parameters comprising weight, height were measured using standardized methods. The BMI was estimated as weight (kg) divided by the square of height (m). The biochemical parameters were accomplished including fasting plasma glucose, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) ,serum cholesterol, serum triglycerides (TG), Low-density lipoprotein-cholesterol (LDL-C), high-density lipoproteincholesterol (HDL-C) Glutathion S-transferase (GST) and superoxide dismutase (SOD). The Estimation of serum fasting glucose, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) ,serum cholesterol, serum triglycerides (TG), Low-density lipoprotein-cholesterol (LDL-C) and high-density lipoproteincholesterol (HDL-C) level by using (cobas c311 Analyzer(s)) but the Measurement some of the enzymatic activities of antioxidant (Glutathion S-transferase (GST) and superoxide dismutase (SOD)) by using (ELISA reader).

Statistical analysis: The cross-sectional in the current study by Using the statistical package for social sciences (SPSS) software for windows, version 26, IBM, US, 2019, and use megastat Data of all participants were entered and analyzed with appropriate statistical tests.

Descriptive statistics were presented as mean and standard deviation (SD) for the continuous variables. Analysis of variances (ANOVA) test was used to compare means of variables for three groups, and student's t test was used to compare means for every two groups.

RESULTS

Effect of metformin or insulin treatments in patients with T2DM.

1- The relationship between of treatment (metformin and insulin) and duration of treatment.

This study indicated of duration of treatment in G2 group was (mean 6.97± 4.96) years, the range of treated in metformin (1-20) years, as shown in table (3.1). while the mean of duration of treatment of G3 group was (mean 10.80 ± 5.86) years, the range of treated in insulin (2-22) years , there was a significant differece group (p≤0.05) as shown in table (1.1).

2- The effect of treatment (metformin and insulin) on fasting blood sugar (FBS).

This result was found the mean of FBS in G2 group was (218.56 ± 100.05) mg/dl, while the mean of FBS of G3 group was (289.05 ± 125.02) mg/dl, there was a significant difference between group (p≤0.05) as shown in table (1.1).

3- The effect of treatment (metformin and insulin) on ALT and AST.

The results of this study were found the mean of serum ALT activity in G2 was (mean 14.91± 8.37) IU/L, while The mean of serum ALT activity in G3 was (mean 12.89 ± 9.61) IU/L, there was no a significant difference between two group (p≤0.05) as shown in table (1.1).

4- The effect of treatment (metformin and insulin) on SOD and GST.

The results of this study indicated mean of serum SOD activity in G2 was (mean 318.52 ± 42.36) IU/L, while The mean of serum SOD activity in G3 was (mean 331.52 ± 11.58) IU/L, there was no a significant difference two groups (p≤0.05) as shown in table (3.3). as well as The mean of serum GST activity in G2 was (mean 117.80 ± 32.16) IU/L, The mean of serum GST activity in G3 was (mean 129.79 ± 19.53) IU/L, there was no a significant difference two groups (p≤0.05) as show in table (1.1).

5- The effect of treatment (metformin and insulin) on lipid profile.

The results of this study indicated mean of serum (cholesterol, TG , HDL, LDL and VLDL) in G2 were (161.85 ± 48.39, 242.43 ± 163.71, 32.59 ± 10.78, 80.77 ± 34.18 and 48.48 ± 32.47) mg/dl respectively, and the mean level of serum (cholesterol, TG , HDL, LDL and VLDL) in G3 were (171.40 ± 32.51, 218.17 ± 103.15, 31.92 ± 8.18 , 95.84 ± 32.65 and 43.63 ± 20.63) mg/dl respectively ,the results was found non a significant difference between all lipid profile biomarkers in the two group (p≤0.05), as shown in table (1.1).

Table 1.1: the effect of treatments kind (metformin and insulin) on some biochemical marker in diabetic patients.

Parameter	G2 group No=32	G3 group No=30	P-value
Age (years)	52.06 ± 8.83	53.07 ± 7.71	0.63
BMI (kg/m2)	29.40 ± 4.84	29.43 ± 3.85	0.97
Duration Of treatment	6.97 ± 4.96	10.80 ± 5.86	≤0.05*
F.B.S(mg/dl)	218.56 ±100.05	289.05 ± 125.02	≤0.05*
ALT U/L	14.91 ± 8.37	12.89 ± 9.61	0.38
AST U/L	21.23 ± 5.98	22.32 ± 9.26	0.58
Superoxide dismutase U\L	318.52 ± 42.36	331.52 ± 11.58	0.10
Glutathione S Transferase (U/L)	117.80 ±32.16	129.79 ±19.53	0.07
CHOLESTEROL mg/dl	161.85 ± 48.39	171.40 ± 32.51	0.36
Triglyceride mg/dl	242.43 ± 163.71	218.17 ± 103.15	0.48
HDL-C mg/dl	32.59 ± 10.78	31.92 ± 8.18	0.78
LDL-C mg/dl	80.77 ± 34.18	95.84 ± 32.65	0.08
VLDL-C (mg/dl)	48.48 ± 32.74	43.63 ± 20.63	0.48

* Significant at P≤0.05.

G2: group of patient with T2DM who are treated with metformin.

G3: group of patient with T2DM who are treated with insulin.

DISSCUSSION

The effect of treatment on fasting blood sugar (FBS): This result may be due to the Metformin is the first-line drug for treatment of type 2 diabetes mellitus, with an excellent safety profile, high efficacy in glycaemic control (36).The pleiotropic properties of metformin suggest that the drug acts on multiple tissues through various underlying mechanisms rather than on a single organ via a unifying mode of action (37). Mitochondrial respiratory chain complex 1 is targeted by metformin and its inhibition is involved in AMP-activated protein kinase-independent regulation of hepatic gluconeogenesis by triggering alterations in cellular energy charge and redox state(37)(38). Metformin might contribute to improvements obesity-associated met inflammation and tissue-specific insulin sensitivity through direct and indirect effects on various resident immune cells in metabolic organs(39). The gastrointestinal tract has an important role in the action of metformin, which modulates bile acid recirculation and enhances the secretion of the glucose-lowering gut in cretin hormone glucagon-like peptide-1 (40)(41). The gut is a novel target in the mechanisms of metformin action and is involved in both the therapeutic and adverse effects of the drug (42)(43). And this a results were matching with the results of (44)(45)(46)(47), while the insulin therapy stimulates the conversion of simple energy units such as monosaccharides (including glucose) and amino acids into complex macromolecules such as proteins, lipids and glycogen. This is accomplished, in part, by increasing glucose uptake in muscle and adipose tissue(48). The majority of insulin-stimulated glucose uptake occurs in skeletal muscle. Where glucose is stored as glycogen, which is mobilized when fuel demands are high or glucose is not abundant. About 10% of insulin-stimulated glucose uptake occurs in adipose tissue, where energy is stored as triglycerides(49).Triglycerides are released from adipocytes as free fatty acids (FFAs) and utilized as an energy source by other

tissues when fuel availability is low(48). And this a results were matching with the results of (L. Blonde,2009)(R. P. Rallapeta,2020) (50)(51).

The effect of treatment on ALT and AST: these result may be due to Metformin has anti-inflammatory effects in the liver that have been linked to weight-reduction(52). Inflammation and oxidative stress in the liver increase the concentration of liver enzymes(53). And this a results were matching with the (54) (55)(56), while the insulin therapy, acts to increase uptake of glucose in the liver , decreasing gluconeogenesis and promoting glucogen synthesis , thus, insulin is not hepatotoxic and has not linked to serum enzyme elevation or instance of clinically apparent liver injury high dose including overdose of insulin and glucose can results in hepatic glucogenosis and serum (57). And this a results were matching with the results of (58)(59). So that this study indicated the same effect of two treatments (metformin or insulin) on the activities of ALT and AST in T2DM patients.

The effect of treatment on SOD and GST: however two treatments (metformin or insulin) same effect on SOD and GST activities in patients with T2DM , these result may be due to many Studies have revealed that administration of metformin stops the production of free oxygen radicals by direct inhibiting of the complex I electron transfer complex chain (NADH ubiquitin oxidoreductase (NADH)(60)(61). It was also revealed that metformin can apply its antioxidant effects by inhibiting NAD (P)H/PKC oxidase pathways(62). The dose-dependent metformin also reduced the level of liver peroxide hydrogen(63) . In these conditions, metformin inhibits oxidative reactions by applying its antioxidant effects. Metformin can play its role through several different mechanisms, including 1) direct trapping of hydroxyl radicals; 2) activating antioxidant enzymes such as catalase, which is the main decomposer of H2O2; and 3) reducing the transcription from NOX4 in long term injection of metformin (64)(65)(66). And this a results were matching with the results of (67), while the insulin therapy the administration of exogenous insulin appears to exert a strong inhibitory effect on activation of oxidative stress, a hypothesis that is in agreement with its anti-inflammatory effect (68)(69). insulin can inhibit inflammatory cytokines and the oxidative stress response. The interaction between cytokines and oxidative stress has also been recently investigated (70)(71), however, oxidative stress can be an initiator of cytokine release and cell damage(72). insulin could prevent the decrease of cell viability mediated by oxidative stress, through suppressing the excessive production of ROS, and inhibit both necrotic and apoptotic cell death in various cell types, including hepatocytes, pancreatic beta cells, neuronal cells, myocardial cell, and endothelial cells(73)(74)(75). Insulin suppresses the magnitude of oxidative, nitrosative, and inflammatory stress and tissue damage responses induced by endotoxin, as evidenced by the inhibition of the increase in nitrite and nitrate, free fatty acids, and thiobarbituric acid reactive substances (TBARS) and a significant reduction in ROS generation(76). And this a results were matching with the results of (77)(59).

The effect of treatment on lipid profile: The metformin and insulin have same effect on the lipid profile biomarkers in patients with type2 DM. these result may be due to Metformin may counter the derangements in lipid metabolism in T2DM through several pathways(78) (79). Through increasing insulin sensitivity, metformin reduces the rate of lipolysis, thereby slowing the conversion of free fatty acids to lipoprotein precursors in the liver (80) (79). By reducing plasma glucose levels, metformin lowers the fraction of irreversibly glycated LDL-C, which is removed less efficiently from the body (81). It has been found that in human hepatoma HepG2 cells, metformin enhances ACC phosphorylation and, as a result, induces the reduction of triglycerides levels. Intracellular triacylglycerol and cholesterol levels were also decreased. This phenomenon can be supported by increased oxidation of fatty acid and its decreased synthesis (18) (82). Metformin also improves dyslipidemia by inducing weight loss in people with impaired glucose metabolism(83).And this a results were matching with the results of (44) , while the Insulin therapy plays a fundamental role in lipid homeostasis by driving most cells to preferentially oxidize carbohydrates instead of fatty acids for energy. It further influences lipid levels by 1) stimulating adipose tissue lipoprotein lipase, resulting in the clearance of chylomicrons and very low-density lipoprotein (VLDL) particles from the circulation with attendant delivery of fatty acids to the adipose tissue; 2) promoting triglyceride synthesis in adipocytes; 3) decreasing lipoprotein lipase activity in the skeletal muscle(84)(85), theraby preventing lipid accumulation in this tissue; and 4) reducing lipolysis by inhibiting hormone sensitive lipase in adipocytes. The net effect of insulin action on lipid metabolism results in a reduction of circulating triglycerides and triglyceride-rich lipoprotein level (86)(85). And this a results were matching with the results of (87)(86).

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