Egypt. J. Chem. **Vol. 64,** No. 6 pp. 2997 - 3003 (2021)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Subgrouping of Type 2 Diabetes Mellitus Patients Based on Proteinuria and Diabetic Control for Treatment and Follow-Up

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Abstract

Patients with type 2 diabetes mellitus (T2DM) exhibit improved symptoms at the start of treatment, but their conditions subsequently deteriorate after a few months of treatment. In the present study, patients treated with glibenclamide and metformin were followed up to evaluate the efficacy of treatment based on some biochemical parameters in T2DM subgroups. The patients with T2DM were subgrouped according to their glycated hemoglobin (HbA1c), sex, urinary albumin to creatinine ratio (UACR), and uric acid UA levels. A total of 662 patients participated in the study, which aimed to follow up with glycated hemoglobin (HbA1c), fasting blood sugar (FBS), uric acid (UA), UACR, and lipid profiles at the beginning of treatment and after 2 and 4 months. Results showed that the best treatment effect occurred when patients were classified according to the UACR and HbA1c. In general, all parameters, especially lipid profile and UA levels, changed when patients exhibit proteinuria compared with those in normal UACR patients. Depending on the glycemic control subgroups, all parameters were higher in patients with poor glycemic control than those with fair glycemic control, except for HDLc, which was lowest in the poor-control patients. The parameters revealed significant improvement ($p<0.05$) in lipids, UA, UACR, and HbA1c after 2 months of treatment but subsequently remained slightly increased after 4 months. The parameters measured by using subgroups were better than those obtained from the whole group. The patients who initially experienced improved symptoms tended to ignore regular treatment and restricted diet, thereby worsening the measured parameters.

Keywords: Diabetes mellitus, uric acid, HbA1c, treatment, and proteinuria

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic illness of multiple etiologies, including environmental and genetic factors, that is characterized by chronic hyperglycemia with disturbances of carbohydrate, protein, and fat metabolism resulting from insulin resistance (IR) and accompanies many sociocultural, physical, social, and emotional effects [1, 2]. More than 380 million people are estimated to develop T2DM by 2025 [3]. T2DM treatment aims to achieve good glycemic control and reduce mortality and the risk of vascular complications [4]. The incidence of cardiovascular disease (CVD) and other related microvascular disorders are associated with routine lifestyle factors in T2DM patients [5].

Different biochemical tests are routinely conducted to investigate the progress of T2DM and monitor its consequences. Hyperuricemia has been previously described as a strong predictor of well-defined cerebrovascular complications in T2DM patients [6]. Metformin (MF) is one of the treatments that also target uric acid (UA) by reducing its production [7]. Hyperuricemia is associated with a high risk of CVD and death in patients with T2DM [8, 9]. Lamanna et al. (2011) showed that MF could protect heart vessels by reducing total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDLc), body weight, and blood pressure [10]. Therefore, patients with T2DM treated with MF and glibenclamide (GBC) must be followed up to optimize glycemic control and prevent long-term complications [11, 12]. Knowledge of these factors can help patients develop targeted interventions to improve glycemic control and prevent diabetes-related complications [13]. Different treatment regimens are used to control the progression of the disease, including diet restriction, hypoglycemic drugs, and exercise [14]. However, approximately half of patients with T2DM in the US cannot reduce their glycated hemoglobin (HbA1c) levels to <7.0% due to the complexity of therapeutic regimens; the lack of information; psychosomatic factors, especially depression and general health system; and costs [15].

Unfavorable lipid profile can forecast glycemic control, represented by the HbA1c level, in patients with T2DM. Monitoring and maintaining lipids within normal ranges and the early diagnosis of dyslipidemia can be used as a defensive measure for ideal long-term glycemic control

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Receive Date: 02 January 2021, Revise Date: 24 January 2021, Accept Date: 14 March 2021

DOI: 10.21608/EJCHEM.2021.56262.3208

[16]. CVD is the major cause of morbidity and mortality in patients with T2DM [17, 18]. Dyslipidemia is common in patients with T2DM and is characterized by elevated TG and a predominance of small dense LDL particles and low high-density lipoprotein cholesterol (HDLc) [19]. Treatment of T2DM with ordinary medications can affect different variables, including the levels of glucose, insulin, HDLc, LDLc, UA, and IR indices [20]. Treatment with hypoglycemic agents led to decreased TC and TG and increased HDLc in patients with T2DM [21, 22]. In the present study, the patients treated with GBC and MF were followed up for 2–4 months. HbA1c, FBS, UA, urinary albumin to creatinine ratio (UACR), and lipid profiles were measured at the start and after 2 and 4 months of GBC therapy. We aimed to define the parameter that is most affected by therapy in T2DM subgroups. Patients with T2DM were subgrouped according to diabetic control, sex, UACR level, and UA level.

Experimental Part

Subjects

The subjects were patients with T2DM receiving outpatient treatment at a private clinic specializing in diabetes in Najaf, Iraq, from December 2015 to April 2017. Oral informed consent for participation in this study was obtained from the patients who were using hypoglycemic agents, and approval was obtained from the Ethics Review Board of the Kufa University number 133/2016. GBC monotherapy with a starting dose of 5–10 mg or GBC in combination with other drugs, mostly 500 mg MF, was then administered. A total of 662 patients were registered. This study was an observational study that proposes to evaluate the efficacy of treatment on some biochemical parameters in patients with T2DM. HbA1c, FBS, UA, UACR, and lipid profiles were measured at the start and after 8 and 16 weeks of GBC therapy. The patients were divided according to the level of UACR level into normal UACR (UACR<30mg/g), microalbuminuria (UACR=30-300 mg/g), and overt albuminuria when UACR>30-300 mg/g. Furthermore, the patients were divided according to the glycemic control into good control (HbA1c<6.2%), fair control (HbA1c=6.2-7.9%), and poor control (HbA1c>7.9%).

Exclusion Criteria: We excluded patients with any thyroid disorders, cancer, and hypertension.

Measurements

Serum glucose and lipid profile, which included TC, TG, and HDLc, were measured spectrophotometrically by enzymatic reactions using ready-for-use kits supplied by Spinreact®, Spain. Serum HDLc was determined after the precipitation of other lipoproteins by the reagent containing sodium phosphotungstate and $MgCl_2$, and the cholesterol contents in the supernatant were measured using the cholesterol kit. Very LDLc (VLDLc) was calculated using the equation TG/2.19, and LDLc was computed based on Friedewald's formula (LDLc=TC − HDLc − VLDLc). HbA1c in whole blood was measured using the i-CHROMA™ HbA1c kit, which is based on competitive immune detection as measured by fluorescence immunoassay. Whole blood was added to the mixture of hemolysis buffer and detection buffer, resulting in red blood cells' hemolysis. The mixture containing HbA1c from the hemolyzed red blood cells and fluorescence-labeled HbA1c peptides from the detection buffer was loaded onto the cartridge's sample well. HbA1c from the blood competed with fluorescence-labeled HbA1c peptides for binding sites on HbA1c antibodies and was fixed on the nitrocellulose matrix. Thus, a high HbA1c concentration produces a low fluorescence signal from HbA1c peptides. The signal was interpreted, and the results were displayed on the i-CHROMA™ reader in % unit.

Statistical analysis

Normally distributed variables were expressed as mean ± standard deviation. The analysis of variance (ANOVA) test was used to compare means of parameters among subgroups of T2DM patients. The difference between groups was considered statistically significant when $p<0.05$. All statistical analyses were executed using SPSS Statistics software (version 23, 2015), IBM, USA. Figures were plotted using Excel (Microsoft Office 2016).

Results and Discussion

Table 1 represents the level of the parameters in patients with T2DM, who were subgrouped according to normal UACR (UACR<30 mg/g), mild microalbuminuria (UACR=30–300 mg/g), and proteinuria (UACR>300 mg/g). In general, all parameters changed when the patients exhibited proteinuria compared with those with normal UACR. T2DM patients are at risk for elevated UACR, an early indicator of diabetic nephropathy (DN). Therefore, subdividing patients into normal or abnormal according to the UACR value is necessary because UACR is independently associated with an increased risk for various CVDs [23]. The level of the parameters in patients with T2DM, who were subgrouped according to the UACR level, is presented in Table 1. Only 274 out of 662 patients with T2DM were normal regarding the UACR level. Most of the patients exhibited microalbuminuria (n=282) and overt proteinuria (n=106). These results indicated poor glycemic control, which leads to kidney tissue damage [24], as concluded from FBS and HbA1c. Furthermore, patients with DN demonstrate dyslipidemia and hyperuricemia. These results were previously observed in a study showing a progressive increase in UACR as HbA1c levels increase [25, 26]. In the current study, dyslipidemia also worsened as the UACR increased (Table 1). The correlation between UACR and lipid profile components has been observed [27, 28]. Patients with T2DM and microalbuminuria present inadequately controlled dyslipidemias. Increased LDLc and overall lipid-lowering clinical goals are potential precautions against DN [29]. Dyslipidemia is characterized by low HDLc, elevated TG, and a predominance of small dense LDL particles and is common in patients with T2DM[8].

The level of the parameters in patients with T2DM, who were subgrouped according to the glycemic control, expressed as good control (HbA1c<6.2%), fair control (HbA1c=6.2-7.9%), and poor control (HbA1c>7.9%) is presented in Table 2. In general, all parameters were higher in the poor-control patients than the good- and fair-control patients, except HDLc, which was lowest in the poor-control patients. Most of the patients in this study exhibited poorly controlled hyperglycemia. The awareness in general personal health is low in Iraq. The poor-control group demonstrated higher dyslipidemia and serum UA than the good- and fair-control groups. Patients with T2DM may experience chronic microvascular complications, such as diabetic retinopathy (DR) and DN, during their lifetime

[13]. The mean level of HbA1c in patients with T2DM is 8.97%, and 1/5 of the patients featured good glycemic control (HbA1c ≤7%). The factors associated with good glycemic control are old age, high medication adherence, duration of disease, and good health literacy [13]. Serum UA concentration is associated with DR, DN, and albuminuria severity in T2DM [30]. In the current study, GBC and/or MF exhibited no significant difference in the serum UA level in patients with T2DM, consistent with other studies [31, 32]. Also, no significant difference between parameters when patients were taken GBC alone or with NF.

Table 1. Level of the parameters in T2DM patients sub-grouped according to the UACR level

Parameter	UACR<30 mg/g (N=274)	UACR=30-300 mg/g (N=282)	UACR>300 mg/g (N=106)	p-value
Age (Year)	54.21±5.39	58.17±11.67	67.51±10.80	B
Sex (M/F)	174/100	134/148	45/61	A, B, C
FBS (mg/dl)	226.28±43.71	276.80±81.92	312.52±67.66	A, B, C
HbA1c (%)	7.93±1.82	8.28±1.36	8.4±2.13	B
Creatinine (mg/dl)	0.84±0.26	1.06±0.22	1.4±0.45	B
Urea (mg/dl)	36.46±4.25	38.84±6.40	43.2±9.87	B, C
TC (mg/dl)	202.84±33.8	222.01±17.62	249.9±57.29	A, B, C
TG, F (mg/dl)	128.62 ±27.12	177.12±36.24	202.4±62.60	A, B, C
TG, M (mg/dl)	144.27 ±31.22	192.98±41.10	223.7±54.31	A, B, C
HDLc (mg/dl)	41.86±8.86	38.31±9.73	34.1±6.13	B
LDLc (mg/dl)	136.42±11.47	147.62±21.87	168.5±28.60	B, C
UA, F (mg/dl)	5.13±1.37	5.40±1.62	5.73±1.81	B
UA, M (mg/dl)	5.71±1.20	6.44±1.84	7.31±2.24	B, C

A=Significant difference (p<0.05) between UACR<30 & UACR=30-300 group. B= Significant difference (p<0.05) between UACR<30 & UACR>300 group. C= Significant difference (p<0.05) between UACR=30-300 & UACR>300 group. UACR: Urinary albumin/creatinine ratio, FBS: Fasting blood glucose, HbA1c: glycated hemoglobin, TC: total cholesterol, TG: triglycerides, HDLc: High-density lipoprotein cholesterol, LDLc: Low-density lipoprotein cholesterol, UA: uric acid.

Table 2. Level of the parameters in T2DM patients sub-grouped according to the HbA1c level

Parameter	Good Control HbA1c<6.2% (N=112)	Fair Control HbA1c=6.2-7.9% (N=162)	Poor Control HbA1c>7.9% (N=388)	p-value
Age (Year)	52.83±7.66	57.67±9.18	62.81±9.79	A, B, C
Sex (M/F)	69/43	91/71	237/151	A, B, C
FBS (mg /dl)	191.33±32.22	288.74±64.85	294.47±58.11	A, B
Creatinine (mg/dl)	0.84±0.36	0.92±0.33	1.37±0.51	B, C
Urea (mg/dl)	34.32±5.57	38.94±7.26	40.38±8.86	A, B
TC (mg/dl)	175.81±26.40	187.94±37.17	228.02±57.76	B, C
TG, F (mg/dl)	118.23 ±24.97	159.16±27.85	189.15±57.42	A, B, C
TG, M (mg/dl)	138.34 ±27.66	172.07±385	217.02±48.19	A, B, C
HDLc (mg/dl)	39.45±6.27	38.83±7.27	32.02±5.71	B, C
LDLc (mg/dl)	114.36±21.52	121.71±27.33	133.17±31.45	A, B, C
UA, F (mg/dl)	4.28±1.16	5.68±1.71	5.83±1.58	A, B
UA, M (mg/dl)	5.61±1.20	6.71±1.78	7.11±2.16	A, B

A=Significant difference (p<0.05) between Good Control & Fair Control group. B=Significant difference (p<0.05) between Good Control & Poor Control group. C= Significant difference (p<0.05) between Fair Control & Poor Control group. F: female, M: male, FBS: Fasting blood glucose, HbA1c: glycated hemoglobin, TC: total cholesterol, TG: triglycerides, HDLc: High-density lipoprotein cholesterol, LDLc: Low-density lipoprotein cholesterol, UA: uric acid.

The parameters in Table 3 revealed significant changes (p<0.05) after two months of treatment and different profiles after 4 months of treatment in patients with T2DM. Lipids, UA, UACR, and HbA1c levels improved with treatment. However, as shown in Figure 1, FBS, HbA1c, and TG levels initially decreased but slightly increased after four months of treatment. Table 3 represents the level of the parameters in T2DM patients at baseline and after 2 and 4 months of treatment with GBC and MF. When all of the patients were considered a whole group, a general improvement in measured parameters was observed after 4 months of treatment. When patients feel good, they discontinue drug-taking, and this phenomenon represents one of the important factors leading to the exacerbation of the disease in Iraq. HbA1c declined from 8.3% to 6.6% after 26 weeks of follow-up, although 28.7% of patients do not achieve HbA1c levels <7% [33]. These results are close to the results of the present work. T2DM treatment benefits TC and TG's level, but the results are variable across studies [17, 34]. The concentration of serum UA is highly correlated with DR and DN in T2DM [30]. Diabetic patients exhibit a significantly increased serum UA level compared with controls. In a previous study, GBC improves TG and HDLc levels in patients with T2DM, but a meta-analysis showed that the lipid profile effect is not significant in patients with GBC (p=0.760) [21].

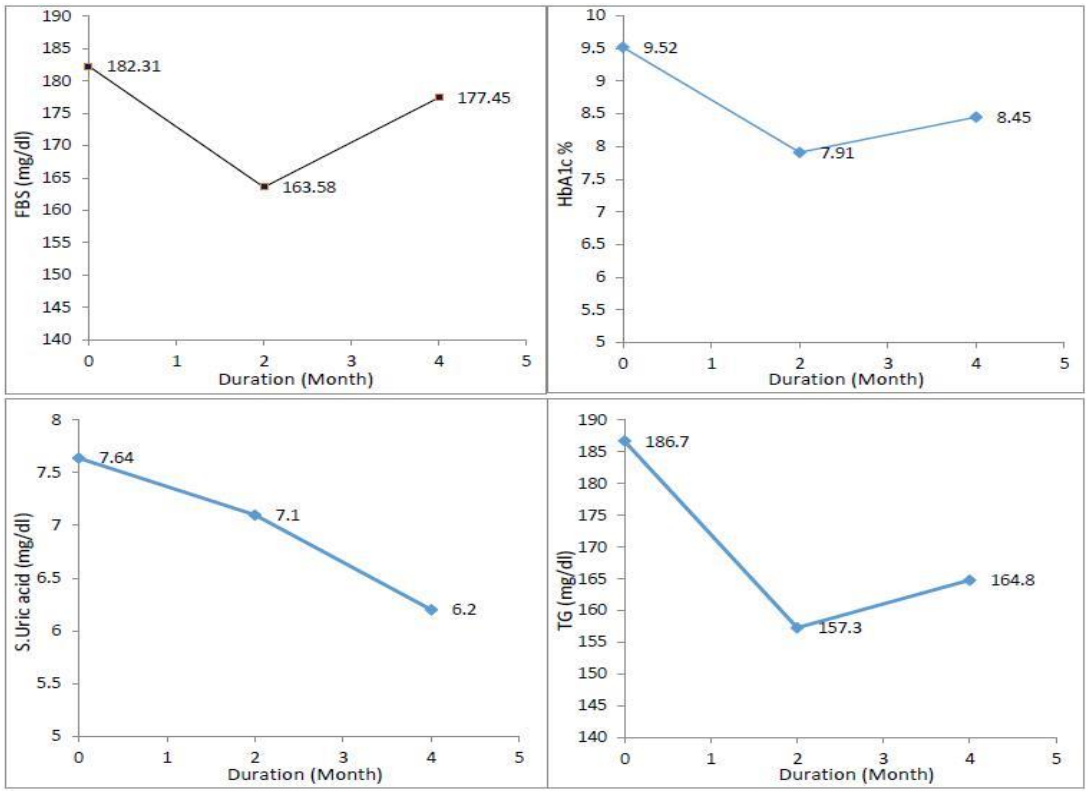

Fig. 1. Changes in FBS, HbA1c, TGs, and UA in diabetic patients after 4 months of treatment

Table 3. Level of some parameters in T2DM patients at baseline, after 2 months, and 4 months of treatment.

Parameter	*Baseline*	*2 Months*	*4 Months*	*p-value*
FBS (mg /dl)	182.33±58.61	163.62±64.91	177.57±32.64	*A, B, C*
HbA1c %	9.51±1.64	7.96±0.98	8.40±1.23	*A, B*
UACR (mg/g)	(88.75)	(84.24)	(56.41)	*B, C*
Creatinine (mg/dl)	0.93±0.34	0.84±0.27	0.80±0.37	*NS*
Urea (mg/dl)	38.28±8.35	361±7.26	37.31±5.89	*NS*
TC (mg/dl)	218.52±57.78	197.77±44.31	188.90±26.52	*A, B, C*
TG (All) (mg/dl)	186.73±57.36	157.37±27.19	164.81±24.78	*A, B, C*
HDLc (mg/dl)	32.52±5.34	33.02±7.72	39.43±6.31	*C*
LDLc (mg/dl)	133.22±31.83	121.47±27.30	114.03±21.13	*A, B, C*
UA (All) (mg/dl)	7.62±1.51	7.14±1.47	6.24±1.10	*A, B*

A=Significant difference (p<0.05) between Baseline & 2 Months treatment group. B=Significant difference (p<0.05) between Baseline & 4 Months treatment group. C= Significant difference (p<0.05) between 2 Months treatment & 4 Months treatment group. NS=Non-significance. UACR: Urinary albumin/creatinine ratio, FBS: Fasting blood glucose, HbA1c: glycated hemoglobin, TC: total cholesterol, TG: triglycerides, HDLc: High-density lipoprotein cholesterol, LDLc: Low-density lipoprotein cholesterol, UA: uric acid

The results in Table 4 reveal the level of the parameters in T2DM patients at baseline and after 2 and 4 months of treatment. The poor-control group exhibited worse levels of FBS, TC, and TG compared with the fair-control group. HbA1c is an index for beta cell function in T2DM patients [35]. Therefore, increased HbA1c indicates that the beta cells work overtime to compensate for insulin deficiency

and are subsequently exhausted and depleted faster than the fair control groups. Elevated atherogenic lipoproteins carrying bad cholesterol in the blood represents a major risk factor for CVD, especially in patients with T2DM who demonstrate dyslipidaemia and IR [36, 37]. The cholesterol contained within apolipoprotein B particles, which are also referred to as non-HDLc, is strongly associated with atherosclerosis's pathogenesis [36]. Although some effects may be significant, many drugs produce relatively small alterations in the lipid profile [38]. CVD is the major cause of morbidity and mortality in patients with T2DM [18]. Importantly, heart failure is frequent in T2DM, and several glucose-lowering medications may increase the risk of heart failure [39]. GBC is associated with significant reductions in TC [40]. Even with good glycemic control, HbA1c<7, these patients possess twice the mortality risk than the general population [18]. When patients were divided into male and female groups, only TG and UA

showed a significant difference in the TGs and UA in T2DM patients after 2 and 4 months of treatment, as seen in Figure 2. Some differences between gender can be attributed to lifestyle habits, sociodemographic, genetics, and multi-factorial risk factors [41, 42]. McCollum et al. (2005) reported that males are usually engaged in physical activity more than females, although females are healthier and diet-restricted than males [43]. Psychosocial factors can be considered as an important factor in the development and progression of T2DM [44].

Biomedical basic study and clinical research in endocrinology must be beneficial to both genders at a balanced level. In Iraq, the psychological and social factors are important in the development, progression, and treatment of diabetes [45].

Conclusion

The classification of T2DM patients into subgroups is informative and provides information that is different from that obtained using the results of a whole group. Results indicated general improvement in the level of the measured parameters after 2 months of treatment. However, FBS, HbA1c, and TG levels initially decreased after 2 months of treatment but returned to slightly increased levels after 4 months of treatment. When patients feel good, they discontinue their medications. This phenomenon represents an important factor leading to the exacerbation of the disease in Iraq.

Table 4. Level of the parameters (in mg/dl) in T2DM patients at baseline, after 2 months, and 4 months of treatment

Months	FBS		UA (Overall)		TG (Overall)		TC	
	Fair	Poor	Fair	Poor	Fair	Poor	Fair	Poor
Baseline	194.40	286.54	6.53	7.62	211.74	248.63	211.71	248.60
2	167.51	192.72	5.10	7.17	140.33	174.61	140.32	174.67
4	172.74	214.67	5.39	6.26	164.67	191.90	164.69	191.96

UACR: Urinary albumin/creatinine ratio, FBS: Fasting blood glucose, TC: total cholesterol, TG: triglycerides, UA: uric acid.

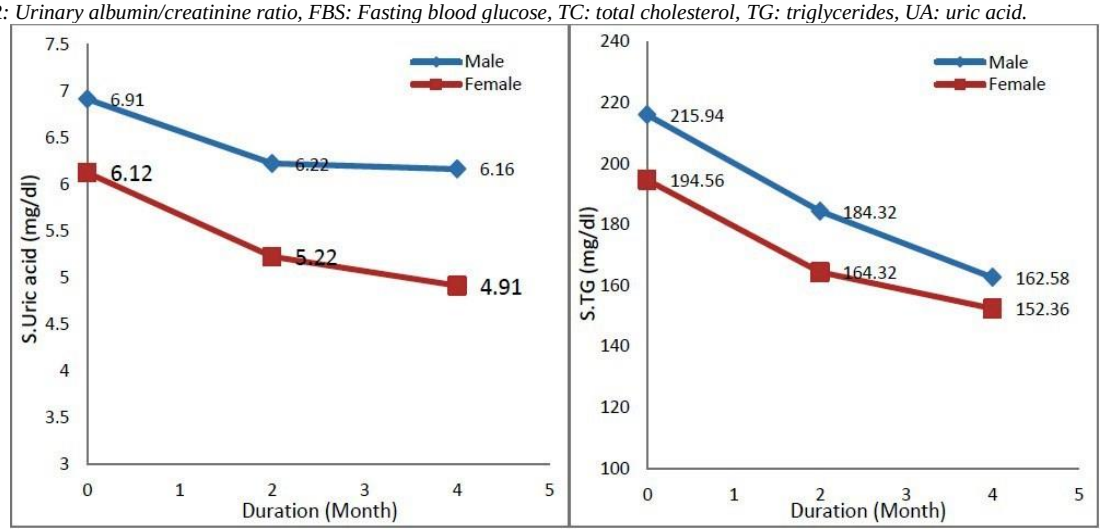

Fig. 2. Changes in TGs, & UA in male and female diabetic patients after two, and four months of treatment

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تصنيف مرضى السكري النوع الثاني فرعيا وفق زيادة البروتين في البول (الإدرار) مقارنة مع الأصحاء لأجل متابعة العلاج

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الخلاصة

يظهر مرضى داء السكري من النوع الثاني (T2DM) تحسنا ملحوظا عند بدء العلاج ولكن حالاتهم تتدهور بعد ذلك خلال بضعة أشهر من العلاج. في هذه الدراسة، تمت متابعة المرضى الذين عولجوا بدوائي الكليبينكلاميد والميتفورمين لتقييم فعالية العلاج بناءً على نتائج بعض المتغيرات الكيموحيوية المقاسة في المجموعات الفرعية لداء T2DM. تم تصنيف المرضى الذين يعانون من T2DM إلى مجموعات فرعية استنادا إلى نتائج الهيموجلوبين السكري (HbA1c) والجنس ونسبة الألبومين إلى الكرياتينين في الإدرار (UACR) ومستويات حامض اليوريك (UA). اشترك في هذه الدراسة 662 مريضا وتمت متابعة تراكيز المواد التالية في دمهم HbA1c، سكر الدم الصائم (FBS) ، UA، UACR، وأنماط الدهون في بداية العلاج وبعد مرور شهرين و أيضا بعد 4 شهور.

أظهرت النتائج أن أفضل تأثير للعلاج يحدث عندما يتم تصنيف المرضى اعتمادا على قيم UACR وHbA1c. وبشكل عام تغيرت جميع المعلمات، وخاصة مستويات الدهون و UA في المرضى الذين لديهم بروتين في الإدرار مقارنةً باللذين ليس لديهم بروتين في إدرارهم. كما ترتفع تراكيز كل المواد المقاسة عند المرضى الذين ليس لديهم سيطرة على مستوى السكر مقارنة بالمرضى المسيطرين على مستويات السكر في دمهم عدا مستويات البروتينات الدهنية عالية الكثافة HDLc التي أظهرت انخفاضا عند المرضى غير المسيطرين على السكر في دمهم. بعد مرور شهرين من العلاج انخفضت تراكيز UA و UACR و HbA1c وبعد أربعة اشهر من العلاج لم ينخفض اكثر بل بقي محافظا على هذا الانخفاض اعتمادًا على المجموعات الفرعية للتحكم في نسبة السكر في الدم. كانت المعلمات التي تم قياسها باستخدام المجموعات الفرعية أفضل من حيث الفروق من تلك التي تم الحصول عليها عندما اخذ كل المرضى كمجموعة واحدة. يميل معظم المرضى الذين تحسنوا في بداية العلاج إلى تجاهل العلاج المنتظم والنظام الغذائي المقيد، وبالتالي تفاقم نتائج المتغيرات المقاسة.