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RESEARCH ARTICLE

EFFECT OF DIFFERENT THERAPUTIC REGIMENS OF DIABETIS MELLITUS ON RENAL FUNCTION

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ABSTRACT

Diabetes mellitus (DM) is a metabolic disorders which is characterized by chronic hyperglycemia with disturbances of carbohydrates, fats and proteins metabolism resulting from defect in insulin secretion, insulin action, or both causing a significant disturbance of water and electrolytes homeostasis. This is a case control study conducted on 150 diabetic patients of both sexes, 87 (58%) were males and 63 (42%) were females, 50 patients were only on insulin therapy (group 1), 50 patients were only on oral hypoglycemic agent therapy (group 2) and 50 patients were on insulin and hypoglycemic agent therapy (group 3). Renal function test (blood urea, serum creatinine and serum electrolytes) were measured for all patients and compared with each other and with 50 apparently healthy control. Regarding the results of renal function parameters, there were higher levels of serum urea (5.43) mmol/L and creatinine (82.3) μ mol in group 3 ($p<0.001$,$p<0.05$) respectively, with higher values of $S.Na^+$ (142.36) mmol/L and K^+ (5.15) mmol/L in group 2 ($p\leq0.001$, $p<0.05$) respectively, all in comparison with the control group. There was no significant difference in S.urea and S.creatinine level in all groups while significantly higher level of $S.Na^+$ and $S.K^+$ was found in group 2 ($p<0.001$). A part from significant higher level of S.creatinine in males of group 3 (86.75) μ mol ($p<0.001$), there was no significant difference in all other parameters between males and females. In group 1 S.urea (6.23) mmol/L and $S.K^+$ (4.96) μ mol were higher in those with 5-10 years of disease duration ($p<0.05$), with higher level of $S.Na^+$ (145.0) mmol/L in those of < 5 years of disease duration ($P<0.05$) in group 2, while no significant difference was seen in group 3. Also ultrasonography had shown no significant differences between the patients groups themselves and between them and the control group.

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INTRODUCTION

Insulin deficiency and/or resistance results in chronic hyperglycemia, usually is accompanied by glycosuria and other biochemical abnormalities expressed as a wide range of clinical presentation ranging from asymptomatic patient with relatively mild biochemical abnormalities to patient admitted to hospital with severe metabolic decompensation of rapid onset that has led to coma.

The WHO (1999) Criteria Aiding in Diagnosis of Diabetes is:

Categories	FPG mmol/L	2-hr post oral glucose
Normal	<6.0	<7.8
IFG and normal glucose tolerance	6.0-7.0	<7.8
Normal fasting glucose and IGT	<6.0	7.8-11.1
IFG and IGT	6.0-7.0	7.8-11.1

In Mosul City prevalence of the disease among people aged sixty to sixty nine years is 21%. Weighted prevalence of people age thirty to sixty nine is 9%. In 2001 the prevalence in Mosul was 9.1%, 10.35% when WHO criteria and ADA criteria for diagnosis were used respectively. The ratio of type I to type Π in Mosul is approximately l:10. The diabetic patient is susceptible to a series of complications that cause morbidity and premature mortality including; Circulatory abnormalities (atherosclerosis, coronary artery disease, stroke, cardiomyopatyh), Diabetic retinopathy, Diabetic nephropathy, Diabetic neuropathy, and Diabetic foot ulcer.

Diabetic Nephropathy: It is a chronic progressive kidney disease, that is considered to be a major cause of morbidity and mortality in patients with DM. Diabetes mellitus is the most common cause of renal failure that accounts for more than 40% of new cases, and 20% of patients receiving renal replacement therapy. Diabetic nephropathy (DN) is the single largest cause of End Stage Renal Disease (ESRD), mainly in the Western World. Although it is less common as a long-term complication of DM than coronary arteries diseases and stroke but its treatment is life long and expensive. It affects 20-40%

of all patients with DM developing in 35% of type I and 15-20% of type Π. According to the report by the WHO, the prevalence of DN after 15 years of DM is 17.7-56.6% in men and 11.9-71.1% in women. It is more common in Asian diabetics than in white diabetics, with also higher incidence among blacks than white. This is due to the higher prevalence of DM among blacks and Africans. About 25% of patients in dialysis units have DN, which eventually affects about one third of those with type I and 5-10% of those with type Π diabetes. Natural History and Clinical Course of Diabetic Nephropathy: Diabetic nephropathy occurs in two forms: Diffuse and Nodular, which often occur in combination and in an advanced case it is associated with tubular atrophy and interstitial fibrosis. The natural history can be classified into preclinical and clinical phases, which pass into the following stages.

Stage of Hyperfiltration: It is present at the time of diagnosis of DM that is characterized by polyuria and normal blood pressure. It is caused by an increase in blood flow through the glomeruli and an increase in glomerular filtration rate (GFR) of about20-50% above that of age matched non-diabetic controls, with an increase in the size of kidney to the extent of 20%. Some remains in stage 1 and others pass to the next stage after several years. Others can reverse the GFR and kidney size by good glycemic control. Albumin excretion rate (AER) may increase but this is reversible.

Stage of Early Glomerular Lesion: It is characterized by normal blood pressure and normal albumin excretion rate (AER) in the first 5 years (i.e. <20 µg/min or 30 mg/24 hr. The GFR remains elevated or at near normal level, it is a reversible stage that is characterized by structural lesion in the glomerular basement membrane (GBM) with thickening and increase in mesangial matrix.

Stage of Incipient Nephropathy: In healthy kidney, over 99% of filtered albumin is reabsorbed by mechanism near to saturation. Small increase in vascular permeability results in an increase in filtered albumin that is presented to the renal tubules and results in large urinary albumin loss. So the hallmark in this stage is an increase in urinary AER in an average of 20-200 µg/min which is termed as microalbuminuria, that is stabilized when HbA is reduced. Other important finding is high blood pressure with high GFR which is declined with the proteinuria.

Stage of Clinical Nephropathy: The GFR is usually < 75 ml/min. Clinically proteinuria is called overt proteinuria or dipstick positive proteinuria which is urinary albumin excretion (UAE) > 200 µg/min or > 300 mg/24hr or called macroalbuminuria. This proteinuria is advanced into nephritic range proteinuria which is defined as persistent proteinuria > 3000 mg/24hr. It is of glomerular origin and hypertension becomes more established. Histologically there is a characteristic diffuse and nodular intercapillary sclerosis.

End Stage Renal Diseases (ESRD): It is seen in DN 2-3 years after nephrotic range proteinuria. Hypertension is universal and it is important to state that nephrotic range proteinuria which has extensive glomerular damage usually develops nephrotic syndrome. Progression through these stages is rather predictable because the onset of type 1 DM can be identified and most patients are free from age related medical problems. It is estimated that 5-15% of type Π diabetics passes through these stages but the live time is less clear than in type I diabetics.

Glycemic Control: Hyperglycemia is suggested to play a role in the pathogenesis of glomerular hyperfiltration in type I DM. The metabolic control has been long hypothesized as a contributor to the development of DN, and only in recent years that this hypothesis had been proven. A number of observations have shown a correlation between glycemic control and various levels of albuminuria and decline in GFR. The Diabetes Control and Complication Trial (DCCT) has confirmed that intensive insulin therapy and improved metabolic control in patients with type I DM delay the onset and slow the progression of clinically important microvascular complications.

Duration of Diabetes Mellitus: The annual incidence of DN rises rapidly over the first 15-20 years of DM then sharply decline, and about half of patients with DM develop DN after 30 years duration. This means that the cumulative exposure to DM will increase the risk to develop Diabetic Nephropathy.

Racial Factors: The African-Americans, American Indians and Hispanic American develop DN and kidney disease at higher rates than average but these were not explained. The incidence of diabetic ESRD is 3 times greater in black American than in whites. Type Π DM accounts for most of this risk

Diagnosis of DM: The diagnosis of symptomatic diabetes is not difficult. The symptoms of increased thirst, polyuria, polyphagia, and weight loss coupled with an elevation of the plasma glucose level are virtually pathognomonic, when diabetes is suspected in an asymptomatic patient, the primary diagnostic test is measurement of the fasting plasma glucose concentration. If the value is not elevated, an oral glucose tolerance test can be done. And if the patient has symptoms indicative of diabetes mellitus and a fasting venous plasma glucose greater than 8.0 mmol/L or random venous plasma glucose greater than 11.0 mmol/L then glucose tolerance test is unnecessary as the patient has diabetes. Assessment of glycemic control comprises two areas: home and hospital monitoring which is done in outpatient clinics.

Home monitor include urine test and blood glucose test. Urine test by dipstix has major limitation particularly in type I but also in type Π where raised renal threshold for glucose may mask persistent hyperglycemia. Urine test although traditional but it is messy, inaccurate and the cost of home monitory can be reduced by abandoning urine test and direct the patients toward blood test, using reagentstrips and measuring glucose levels only three to four times a week at different times of a day and bring their records to the clinic to adjust their treatment, hospital monitoring is done by testing blood glucose level either upon fasting or random occasion and glycated hemoglobin measurement.

Management of DM: Treatment of diabetes mellitus involves changes in lifestyle and pharmacological intervention with insulin or oral glucose-lowering drugs. In type I diabetes, the primary focus is to replace insulin secretion; lifestyle changes are required to facilitate insulin therapy and optimize health. For most patients with type II diabetes, changes in lifestyle are the cornerstone of treatment. Pharmacologic

intervention represents a secondary treatment strategy for individuals unable to adopt lifestyle changes, although therapeutic strategies for the two forms of diabetes differ. The short term and long term goals of treatment are identical. The treatment goals are divided as follows:

Short term:

- Restore metabolic control to be as close to normal as possible.
- Improve sense of well-being.
- Long term to minimize risk of diabetic complications which includes :
- Accelerated atherosclerosis.
- Microangiopathy (retinopathy, nephropathy).
- Neuropathy.

The blood glucose control is more effective in preventing the initial development of microvascular complications than in preventing the progression of complication once they have become established, this finding underscores the need for aggressive treatment as soon as type II diabetes is diagnosed.

Aim of the study: The present study is aimed to determine the association between some biochemical markers representing the renal function tests with the type of treatment of diabetes and its duration.

Objectives of the study

- To determine the relationship between insulin therapy, oral hypoglycemic drugs and combination therapy in diabetic patients.
- To identify the correlation among serum urea, serum creatinine, serum Na^+, serum K^+ in those diabetic patients.
- To compare these measured parameters in diabetic patients with the control group.
- To assess the effect of duration of therapy on these parameters.

PATIENTS AND METHODS

The patients included in this study were divided into 3 groups in addition to the fourth control group;

Group 1: Diabetic patients on only insulin therapy: 50 patients, duration of treatment ranged from 1-24 years, mean (6.62±6.1), 29 (58%) were male whose ages ranged from 15-60 years (mean 35.7±16.8) and 21 (42%) were female whose ages ranged from 15-65 years (mean 39.8±14.2).

Group 2: Diabetic patients on oral hypoglycemic therapy: 45 patients were on sulphonylureas, 27 (60%) were male whose ages ranged from 27-70 years, mean (47.6±11.6) and 18(40%) were female whose ages ranged from 30-65 years (mean 49.7±9.6) ,the doses of the drug are ranged from 2.5-15 mg/day. Five (10%) patients were on metformin (Biguanide) therapy, all were males whose ages ranged from 41-60 years (mean 49.6±7.7). The doses of the drug ranged from 500-1500 mg/day.

Group 3: Diabetic patients on combination therapy: 50 patients on combination therapy were identified. Duration of treatment ranged from 0.5-17 years (mean 6.07±3.68), 26 (52%) were male whose aged ranged from 30-60 years (mean 47.4±8.75) and 24 (48%) were females whose ages ranged from 45-60 years (mean 51.7±5.18).

Group 4: Fifty adults were used as controls, 22 (44%) were males with age range from 15-70 years (mean 37.3±15.7), 28(56%) were females in the age range from 15-55 years (mean 33.5+14.4) ,these groups consist of apparently healthy individuals and were selected from two different sources:-

- Apparently healthy individuals who were attending Al-Wafaa clinic center for checking and proved to be not diabetic after testing their fasting blood glucose.
- Students of Mosul College of Medicine in different years of graduation.

Specimens

Fasting blood samples were obtained from all patients and control group included in this study by antecubital venepuncture, between 9 – 11 a.m, about (7ml) of blood was obtained after 12 hrs fasting. The blood transferred into disposable plain tube, left for 15-30 minutes at 37 ^oC for clot formation in water bath, then serum was separated by centrifugation at 3000 rpm for 10 min, and the sera were frozen at -20 ^oC and kept for analysis at weekly patches.

Sera were used for enzymatic spectrophotometric estimation of the following biochemical parameters :-

- S. urea.
- S. creatinine.

Flame photometer were used for estimation of S.Na+ and S.k+.

All biochemical analysis were performed in the central lab. of Ibn- Sena general hospital in Mosul City.

Statistical Analysis

The following statistical methods were used for the analysis of data

- Standard statistical methods were used to determine the mean, median, standard deviation (SD) and range (minimum –maximum).
- Paired student Z-test was used to compare results for various biochemical parameters among subjects of the same group.
- Unpaired student Z-test was used to compare results of various biochemical parameters among subjects of different groups.
- ANOVA analysis was used to identify group (s) responsible for statistical difference through comparison.
- Multiple logistic analysis was used to examine the association between the dependable and independent variables.
- Chi-squared test using 2X2 contingency table was used to compare any two groups.
- All values quoted as the mean ±SD. Differences between observations were considered not significant at $P>0.05$.

RESULTS

Serum urea was higher than control in group 3 and the difference was significant ($P<0.01$), while no significant

difference was found in group 1 and 2 (Table I). Serum creatinine was higher in group 3 and the difference was significant (P<0.05) while no significant difference in group1 and 2 in comparison with control group (Table I). Serum sodium concentration was higher in group 2 and the difference was significant (p≤0.001), while there was no significant difference in group 1 and 3 in comparison with control group (Table I).

Serum potassium concentration was higher in group 2 and the difference was significant (p<0.05), while there was no significant difference in group 1 and 3 (Table I). Regarding serum urea and serum creatinine no significant difference was found among three groups (Table II). Regarding serum sodium and potassium, they were significantly higher in group 2 (P<0.001) (Table 2). The measured parameters between the different groups according to the sex had shown that creatinin was higher in males in group 3 (p<0.001) (Table 3).

Table 1. A Comparison of Measured Parameters between Control and Diabetic Patients on Different Therapies

Parameters	Control (n=50)	Group 1 (n=50)	Group 2 (n=50)	Group 3 (n=50)	p-value
Urea (mmol/L)	4.70 ± 1.10	5.19 ± 1.80	5.36 ± 1.99	5.43 ± 1.26**	P<0.01
Creatinine (µmol/L)	76.38 ± 10.90	76.68 ± 16.36	76.40 ± 17.14	82.30 ± 15.02*	P<0.05
Na+ (mmol/L)	139.36 ± 3.34	138.96 ± 3.39	142.36 ± 5.03***	140.50 ± 3.15	P≤0.001
K+ (mmol/L)	4.85 ± 0.67	4.70 ± 0.63	5.15 ± 0.54*	4.81 ± 0.63	P<0.05

* Significant difference from control at p<0.05, ** at p<0.01, *** at p ≤0.001

Table 2. A Comparison of Measured Parameters among Diabetic Patients on Different Therapies

Parameters	Group 1	Group 2	Group 3	p-value
Urea (mmol/L)	5.19 ± 1.80 a	5.36 ± 1.99 a	5.43 ± 1.26 a	p>0.05 (NS)
Creatinine (µmol/L)	76.68 ± 16.36 a	76.40 ± 17.14 a	82.30 ± 15.02 a	p>0.05 (NS)
Na+ (mmol/L)	138.96 ± 3.39 a	142.36 ± 5.03 b	140.50 ± 3.15 a	P<0.001
K+ (mmol/L)	4.70 ± 0.63 a	5.15 ± 0.54 b	4.81 ± 0.63 a	p<0.001

Means with different letters (a, b) horizontally have significant difference at p< 0.05.

Table 3. A Comparison of Measured Parameters among Diabetic Patients on Different Therapies According to the Sex

Parameters	Sex	Group 1		Group 2		Group 3	
		Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value
Urea (mmol/L)	M	5.55 ± 1.29	p>0.05 (NS)	5.21 ± 1.40	p>0.05 (NS)	5.48 ± 1.22	p>0.05 (NS)
	F	5.16 ± 2.56		5.17 ± 2.27		5.34 ± 1.36	
Creatinine (µmol/L)	M	77.62 ± 12.84	p>0.05 (NS)	79.14 ± 15.89	p>0.05 (NS)	86.75 ± 15.05	p<0.01
	F	75.08 ± 21.04		73.29 ± 16.77		74.39 ± 11.56	
Na+ (mmol/L)	M	142.73 ± 5.76	p>0.05 (NS)	177.21 ± 203.66	p>0.05 (NS)	140.34 ± 2.90	p>0.05 (NS)
	F	141.96 ± 4.18		138.43 ± 3.26		140.78 ± 3.62	
K+ (mmol/L)	M	5.19 ± 0.61	p>0.05 (NS)	6.15 ± 8.46	p>0.05 (NS)	4.87 ± 0.66	p>0.05 (NS)
	F	5.10 ± 0.45		4.83 ± 0.60		4.70 ± 0.56	

Table 4. The Effect of Duration of Therapy on the Measured Parameters for Group 1

Duration (yr)	Mean ± SD			Significance
Parameters	<5	5-10	>10	
Urea (mmol/L)	4.54 ± 1.06	6.23 ± 1.35	5.56 ± 2.44	P<0.05
Creatinine (µmol/L)	71.83 ± 14.93	77.78 ± 13.94	82.94 ± 18.01	p>0.05 (NS)
Na+ (mmol/L)	138.29 ± 3.62	140.22 ± 3.27	139.24 ± 3.05	p>0.05 (NS)
K+ (mmol/L)	4.47 ± 0.64	4.96 ± 0.52	4.88 ± 0.57	P<0.05

Table 5. The Effect of Duration of Therapy on the Measured Parameters for Group 2

Duration (yr)	Mean ± SD			Significance
Parameters	<5	5-10	>10	
Urea (mmol/L)	5.44 ± 1.60	4.89 ± 1.33	6.25 ± 3.21	p>0.05 (NS)
Creatinine (µmol/L)	73.38 ± 9.88	75.04 ± 15.58	83.64 ± 26.12	p>0.05 (NS)
Na+ (mmol/L)	145.00 ± 6.90	141.48 ± 3.22	140.36 ± 3.50	p<0.05
K+ (mmol/L)	5.34 ± 0.69	5.07 ± 0.46	5.03 ± 0.37	p>0.05 (NS)

Table 6. The Effect of Duration of Therapy on the Measured Parameters for Group 3

Duration (yr)	Mean ± SD			Significance
Parameters	<5	5-10	>10	
Urea (mmol/L)	5.32 ± 1.36	5.31 ± 1.20	5.94 ± 1.02	p>0.05 (NS)
Creatinine (µmol/L)	83.68 ± 14.81	80.69 ± 14.97	81.33 ± 17.05	p>0.05 (NS)
Na+ (mmol/L)	140.16 ± 3.33	140.50 ± 3.25	141.44 ± 2.56	p>0.05 (NS)
K+ (mmol/L)	4.97 ± 0.61	4.64 ± 0.67	4.64 ± 0.53	p>0.05 (NS)

Regarding Sodium and Potassium ions concentrations, no difference was noticed between the studied groups (Table 3). Tables 4, 5, 6 have shown the effect of duration of treatment on the measured parameters in each group, there was some effects of the duration of treatment on some parameters and no effect on others. In group1; serum urea, serum k+ concentration were higher in those with 5-10 years duration ($p<0.005$) (Table 4). In group 2 serum sodium concentration was higher in those with < 5 years duration of therapy ($P<0.05$) (Table 5). In group 3 there was no significant difference in the measured parameters, regarding the duration of treatment (Table 6). Also by ultrasonography examination, there were no significant changes between the patients groups themselves and between the patients and the control group. Means with different letters (a, b) horizontally have significant difference
at $p< 0.05$.

DISCUSSION

Many diabetics may suffer from nephropathy which is approximately equal to cardiovascular disease as causal factors of death. Therefore, some biochemical parameters that related to such complications were measured. Regarding renal function, large number of estimated values of serum urea and serum creatinine were within normal limits. Despite the statistically significant difference in serum urea in both type I and type II diabetics from the control group, the majority of results occupied the upper normal range of this index. However, serum urea and serum creatinine are not sensitive indices of renal function but offer an evidence for the lack of marked renal impairment in these diabetics. Further support to the rarity of renal problems in such Iraqi diabetics was also observed among Sudanese and Saudi diabetics. Atabani et al reported no significant difference in serum urea and serum creatinine in Sudanese diabetics with type I and type II in comparison with control. The upward trend in mean serum urea and creatinine may be explained on the basis that renal function deteriorates slowly. Gradual development of proteinuria accompanied by slowly progressive structural and functional damage occurs over several years and depends on the degree of metabolic control. An additional explanation may be attributed to the increasing age with increasing duration leading to slight elevation of these renal function parameters.

Conclusion

- Serum urea and serum creatinine were significantly higher in group 3 in comparison with the control group, while no significant difference was found in group 1 and 2.
- SERUM sodium and potassium concentration was higher in group 2, while there was no significant difference in group 1 and 3 in comparison with control group.
- Serum urea concentration showed no significant difference among the three groups of diabetics, while creatinine was higher in males in group 3 ($p<0.001$).
- In group 2 serum urea and serum k^+ concentration were higher in those with 5-10 years duration of DM ($p<0.005$) ,while serum sodium concentration was higher in those with < 5 years duration of therapy ($P<0.05$).

Recommendations

- Health education to all diabetic patients and to the general public about the effect of DM on the eye, kidney, nerve and heart is mandatory, highlighting the relation of glycemic control to the slowing of progression of these complications.
- Detailed renal function is a mandatory request, rather than individual, at periodic intervals. And increasing frequency is according to the diabetologist recommendations in patients at high risk for developing micro- and macrovascular complications, aiming to reach at optimal or near optimal levels recommended by the National Cholesterol Education Program (NCEP).

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