

Measurement of Creatinine Clearance in Non-Insulin Dependent Diabetic Patients.

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Abstract

This research was carried out in the period of February to June (2004), to measure creatinine clearance (CCI) in non insulin dependent diabetes mellitus (NIDDM) patients. The influence of age, sex, body mass index (BMI) and duration of the disease on the levels of (CCI) in NIDDM was also subsequently studied.

Blood samples were obtained from two groups:

Group one (Non insulin dependent diabetic group):

Consist of 140 newly diagnosed or known non insulin dependent diabetics.

Group two (Control group):

Consist of 60 apparently healthy individuals.

The mean (CCI) values were significantly lower in NIDDM than in controls ($p < 0.001$). In Both groups: the mean levels of (CCI) in males significantly were higher than females ($p < 0.05$), also the mean levels of serum urea nitrogen (SUN) values were significantly higher in NIDDM than in controls ($p < 0.001$). This study conducted that the mean value (CCI) decrease significantly with increasing the duration of the disease ($p < 0.001$). Versus the mean values of (SUN) increase significantly with increasing the duration of the disease ($p < 0.001$).

KEY WORDS: Creatinine clearance, non insulin dependent diabetes mellitus

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Introduction

Although the long-term complications of non insulin dependent diabetes mellitus (NIDDM) have long been recognized. The major cause of morbidity and mortality of NIDDM is diabetic nephropathy^(1,2). Owing to advances in the diagnosis and treatment has become more effective and is now initiated earlier after the presence of micro albuminuria has been established.

This paper focuses on determining the prevalence of nephropathy in diabetic patients who were followed up in RIZGARY & HAWLER teaching hospitals.

The patients particularly at risk are those with preexisting renal disease or compromised renal perfusion, such as the elderly, those with heart disease, liver disease, diabetes mellitus, and those taking diuretic and anti-hypertensive drugs⁽³⁾.

Great importance is the criteria used for defining renal injury. It is well known that the glomerular filtration rate (GFR) has to decrease by more than 50% of its normal value, for the serum creatinine concentration to increase higher than normal value⁽⁴⁾. Measuring the level of serum creatinine can alert both patient and physician to kidney damage. Creatinine is a waste product of creatine.

The creatinine level is the more advanced for kidney disease, but serum creatinine is generally unable to pick up the earliest stage of kidney disease⁽⁵⁾. So raised serum creatinine is a good indication of impaired renal function, but normal creatinine ratio does not necessary indicate normal renal function⁽⁶⁾.

The measurement of creatinine clearance (CCI) in a hospitalized patient may be fraught with problems, like inaccurate urine collection, in cooperative patient, need for indwelling catheters. The result is usually delayed⁽⁶⁾. More practical method should be used for rapid calculation of the predicted creatinine clearance, using recommended formula proposed by Cockraft and Goult⁽⁷⁾.

GFR is the best single measure of the number of functioning nephrons and is usually estimated routinely by measuring endogenous creatinine clearance⁽⁸⁾. Serum creatinine is a precise measurement and is usually sufficient for following the progress of the patient with renal disease⁽⁹⁾.

Renal impairment is divided into three grades:

1-mild renal insufficiency-the creatinine clearance falls between 40-60 ml/min.

2-moderate renal insufficiency-the creatinine clearance ranges between 21-40 ml/min.

3-advanced renal insufficiency-when the creatinine clearance is below 21 ml/min.

This classification is arranged according to the measured CCL in ml/min, which describes a non acute reduction in GFR. The reference range for normal the creatinine clearance is between 75-125 ml/min.

Urea is formed in the liver from ammonia released by deamination of amino acid, over 75% of non-protein nitrogen are excreted as urea mainly by the kidney.

Urea measurement are widely available and have come to be accepted as giving measure of renal function, however a test of renal function by serum urea level is inferior to that of measuring serum creatinine since 50% or more of urea filtered as the glomerulus's is passively reabsorbed through the tubules and this function increases if urine flow rate decrease as in dehydration^(4, 11).

The main factors induced kidney dysfunction⁽¹²⁾: Age, sex, race, previous renal insufficiency, Specific diseases such as (diabetes mellitus, lupus, and diseases associated with proteinuria), Sodium retention state as, cirrhosis, congestive heart failure (CHF), Dehydration, volume depletion and acidosis, potassium and magnesium depletion, hyperuricemia and hyperuricosuria, and sepsis and shock

The present study is performed to investigate the effect of diabetes on renal

function in different classes of patients mainly those in fourth, fifth, and sixth decades of age (where NIDDM are mostly risk observed).

Subjects and Methods

SUBJECT:

This study was conducted over a period of four months, from February till June 2004, in Rizgary and Hawler teaching hospitals.

The subjects include two groups: Group one (Non insulin dependent diabetic patient group):

Consist of 140 NIDDM patients (60 males and 80 females).

This type was subdivided into three subgroups according to the duration of the disease.

Subgroup(1), less than five years (75 patients), subgroup(2), five to ten years (30 patients), and subgroup(3), more than ten years (35 patients). Details concerning NIDDM are presented in table (1).

Group two (Control group):

Include 60 healthy individuals (30 males and 30 females) with no family or personal history of diabetes, were served as controls. Details concerning NIDDM are presented in table (2).

Sampling:

About 5 to 7 ml of venous blood was withdrawn using disposable syringes. The serum was separated centrifugation nearly immediately (not more than 30 minutes), and was analyzed during the day of getting the particular sample, data collected include; age, sex, weight, and duration of the disease. Biochemical tests include serum creatinine and serum urea.

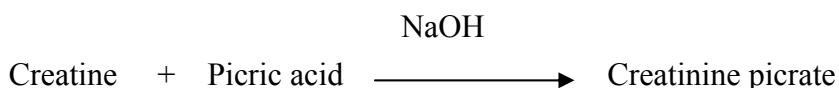
Notes: serum creatinine for determination of creatinine clearance.

Serum urea for determination of serum urea nitrogen (SUN).

Methods:

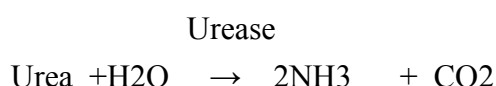
Mesearment of serum creatinine: (Jaffes reagent)

creatinine in alkaline solution reacts with picrate to form creatinine picrate which is red colored complex, the dark color appropriate with the amount of creatinine in serum, and read at 520nm by spectrophotometer(13).



Mesearment of serum urea:

Serum urea concentration was determined enzymatically according to the following reaction.



In the alkaline medium the ammonium ion reacts with phenol and hypochlorite to form green colored indophenol (2,2 dicarboxyl indophenol), the dark color appropriate with the amount of ammonia (NH₃) which is reflected the amount of urea in serum^(13, 14).

For determination of (SUN), the value of serum urea divided to 2.14 because the

$$(140 - \text{Age in years}) \times \text{Weight (Kg)}$$

$$\text{Creatinine clearance (CCI)} = \frac{\text{Creatinine clearance (CCI)}}{72 \times \text{serum creatinine (mg/dl)}}$$

For female individuals the same equation X 0.85

ratio between urea (NH₂CONH₂) to nitrogen (N₂) is 2.14:1 according to those molecular weights ratio 60:28.

Determination of creatinine clearance: (Cockroft&Gault, 1979).

The equation utilized serum creatinine concentration, age, sex, and weight of the patients as follows^(15, 16, and 17).

Statistical analysis:

The statistical evaluation of the results {mean, standard deviation (S.D) and standard error of mean (S.E.M)} were calculated using the scientific calculator (prop-4h-105).

The different variables were compared to each other; simple correlations were tested with the unpaired students test (t-test). Only p<0.05 is regarded as a significant.

Table (1): Details of sex, age, and BMI of diabetes type II (NIDDM).

Sex	Number	Age(year) (Mean±S.E.M)	BMI(Kg/m ²) (Mean±S.E.M)
Male	60	55.6±1.24	24.26±0.362
Female	80	57.36±1.12	25.78±0.42
Both	140	56.34±0.8	25.13±0.29

Table (2): Details of sex, age, and BMI of control group

Sex	Number	Age(year) (Mean±S.E.M)	BMI(Kg/m ²) (Mean±S.E.M)
Male	30	56.73±1.84	24.33±0.57
Female	30	57.67±1.21	25.95±0.776
Both	60	57.25±1.08	25.14±0.49

Results

Table (3) shows the mean (CCl) levels in NIDDM and control groups.

The data obtained indicates that the mean levels of (CCl) of NIDDM was significantly lower than that of control subjects ($p < 0.001$). There was a significant difference ($p < 0.05$) of (CCl ml/min) between males and females.

Table (4) shows the mean serum urea nitrogen (SUN) levels in NIDDM and control groups. The mean (SUN mg/dl) of NIDDM group was significantly higher ($p < 0.001$) than that of control subjects.

Our results revealed that the mean (CCl ml/min) had been decreased significantly ($p < 0.05$) with increasing the duration of the diabetes (table 5).

The data obtained indicated that the mean levels of (SUN mg/dl) had been

increased significantly ($p < 0.05$) with increasing the duration of the disease (table 6).

The data in (table 7) indicated that in control group there is non significantly difference Of (CCl ml/min) between two subgroups according to the obesity, while in diabetic patients the mean levels of (CCl ml/min) in subgroup (BMI>25) was significantly ($p < 0.05$) higher than that of subgroup (BMI<25).

Table (3): Details of creatinine clearance (CCl ml/min) of control and

NIDDM groups:

Groups	Sex	No	creatinine clearance (CCl ml/min) (Mean±S.E.M)
Control	Males	30	92.63±7.5
	Females	30	67.48± 5.86
	Both	60	80.05± 4.89
NIDDM	Males	60	67.44± 3.79
	Females	80	56.56± 3.00
	Both	140	61.22± 2.4

Control	Males	V	Females	Z=2.62	P<0.05
NIDDM	Males	V	Females	Z=2.253	P<0.05
	Control	V	NIDDM	Z=3.122	P<0.05

Note;

V is versus

Z is Z test

Table (4): Details of Serum urea nitrogen (SUN mg/dl) of control and NIDDM groups:

Groups	Sex	No	Serum urea nitrogen (SUN mg/dl) (Mean±S.E.M)
Control	Males	30	17.79±1.09
	Females	30	18.17± 0.83
	Both	60	17.98± 0.68
NIDDM	Males	60	26.47± 1.42
	Females	80	24.01± 0.91
	Both	140	25.13± 0.8

Control	Females	V	Males	Z=1.074	NS
NIDDM	Males	V	Females	Z=1.459	NS
	NIDDM	V	Control	Z=7.182	P<0.001

Table (5): Details of creatinine clearance (CCl ml/min) of control and three subgroups of NIDDM ,according to the duration of the disease.

Groups	No	Controls	No	Subgroup one of NIDDM less than 5 years	No	Subgroup two of NIDDM 5-10 years	No	Subgroup three of NIDDM more than 10 years
Males	30	92.63± 7.5	30	84.3± 5.5	15	53.4± 4.5	15	47.8± 4
Females	30	67.48± 5.8	45	67.9± 4.1	15	42.6 ±4.3	20	41.5 ±4
both	60	80.05± 4.89	75	74.5± 3.4	30	48± 3.2	35	44.2 ±3

Controls	V	Subgroup one	Z=0.941	NS
Controls	V	Subgroup two	Z=5.49	p<0.001
Subgroup one	V	Subgroup two	Z=2.38	p<0.01
Controls	V	Subgroup three	Z=6.28	p<0.001
Subgroup one	V	Subgroup three	Z=6.72	p<0.001
Subgroup two	V	Subgroup three	Z=0.91	NS

Table (6): Mean (SUN mg/dl) (Mean±S.E.M) in control and three

subgroups of NIDDM ,according to the duration of the disease.

Groups	No	Controls	No	Subgroup one of NIDDM less than 5 years	No	Subgroup two of NIDDM 5-10 years	No	Subgroup three of NIDDM more than 10 years
Males	30	17.79± 1.01	30	21.03± 1.45	15	28.13± 1.52	15	47.8± 4
Females	30	18.2± 0.83	45	20.80± 0.93	15	26.62 ±2.03	20	41.5 ±4
both	60	17.98± 0.68	75	20.88± 0.80	30	27.39± 1.25	35	44.2 ±3

Controls	V	Subgroup one	Z=0.941	NS
Controls	V	Subgroup two	Z=5.49	p<0.001
Subgroup one	V	Subgroup two	Z=2.38	p<0.01
Controls	V	Subgroup three	Z=6.28	p<0.001
Subgroup one	V	Subgroup three	Z=6.72	p<0.001
Subgroup two	V	Subgroup three	Z=0.91	NS

Table (7): mean of creatinine clearance (CCl ml/min) (Mean±S.E.M) in obese and non obese in each of control and NIDDM groups:

Groups	No	Non obese BMI<25	No	Obese BMI>25
Control				
Males	19	86.94 ± 9.38	11	102.46 ± 11.23
Females	14	59.03 ± 10.79	14	74.85 ± 5.32
Both	33	75.1 ± 7.38	27	86.17± 5.99
NIDDM				
Males	42	62.7 ± 4.18	18	78.52 ± 7.6
Females	40	49.43 ± 3.68	40	63.68 ± 4.5
Both	82	56.14 ± 2.88	58	68.97 ± 3.95

Control	BMI>25 V BMI<25	Z=1.165	N.S
NIDDM	BMI>25 V BMI<25	Z=2.625	P<0.05

Discussion

The obtained data indicated that the mean levels of (CCI) of NIDDM group was significantly lower than that of control group (p<0.001), table (3), and the mean levels of (SUN) in NIDDM group was significantly higher than that of control group (p<0.001). This is attributed to pre renal, renal and post renal causes. The most important of the pre-renal causes are the cases in which there is dehydration

with reduced volume of body fluids and so of plasma volume which leads to reduced (CCI). This is may be considered as characteristic feature of uncontrolled diabetes mellitus⁽¹⁹⁾. Significant higher values for serum urea nitrogen levels in nephritic diabetic patients and correlated with the deterioration of (CCI) in diabetics possibly has an important influence or raised serum urea level and the progression of diabetic nephropathy⁽²⁰⁾.

In our results there was a significant difference ($p < 0.05$) of CCl values (ml/min) between males and females in both control and NIDDM groups. This is similar results obtained by Alex et al⁽²¹⁾.

Our results revealed that the mean CCl (ml/min) had been decreased significantly ($p < 0.05$) with increasing the duration of the diabetes, and the mean SUN (mg/dl) increased significantly ($p < 0.05$) with increasing the duration of the diabetes. Table (5 and 6) respectively. This results is consistent with those of Rias et al⁽¹⁵⁾, Yokota et al⁽²²⁾, and Levitted et al⁽²³⁾, who found a positive significant correlation between the raised serum creatine and serum urea levels and the duration of the diabetes, and attributed this to reduced CCl (ml/min), and excess breakdown of proteins, that produce an excess of amino acids.

Table (7) provide that the mean levels of CCl (ml/min) in non obese NIDDM patients was significantly higher than that of obese NIDDM patients, this is due to hyperglycemia and glycosuria which cause osmotic diuresis, plasma hyperosmolality, reducing circulating blood volume, reduced renal blood flow and reduced creatine clearance, this features is more obtained in non obese NIDDM patient⁽¹⁹⁾.

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