Creatinine, Cystatin and combined-based equations in assessment of renal functions in type 2 diabetic Egyptian patients

A thesis submitted for Partial fulfillment of the Degree of MSc of Internal Medicine

By

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List of Abbreviations

ADA	**American Diabetes Association**
ACEI	**Angiotensin Converting Enzyme Inhibitor**
AGE	**Advanced glycation end products**
AGEs	**Advanced Glycation End Products**
ARBs	**Angiotensin receptor blocker**
ARBS	**Angiotensin Receptor Blocker**
AT1	**Angiotensin receptor 1**
AUC	**Area Under Curve**
BMI	**Body Mass Index**
BP	**Blood pressure**
BSA	**Body Surface Area**
BUN	**Blood Urea Nitrogen**
CDC	**Centers for Disease Control and Prevention.**
CHD	**Coronary heart disease**
Cr.Cl	**Creatinine clearance**
CVD	**Cardiovascular disease**
DAG	**Diacylglycerol**
DM	**Diabetes mellitus**
DN	**Diabetic nephropathy**
EDTA	**Ethylene Di-amine Tetra-ethyl Acetate**
ELISA	**Enzyme linked immune assay**
ERB	**Endothelin receptor blocker**
ESRD	**End Stage Renal Disease**
GFR	**Glomerular Filtration Rate**
HDLR	**High density lipoprotein receptor**

HMG-COA REDUCTASE	**3hydroxy-3methyl-glutrayl coenzyme A reductase**
IDDM	**Insulin dependent Diabetes mellitus**
IDMS	**isotope dilution mass spectrometry**
LDLR	**Low density lipoprotein receptor**
MDRD	**Modification of Diet in Renal Disease**
NIDDM	**Non-Insulin dependent diabetes mellitus**
PKC	**Protein kinase c system**
RAAS	**Renin-Angiotensin-Aldosterone system**
ROS	**Reactive oxygen species.**
TGF	**Transformation growth factor**

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Abstract

Diabetic nephropathy is the principal single cause of end-stage renal disease (ESRD).

The most important parameter in the clinical evaluation of kidney function is the glomerular filtration rate (GFR), which is generally accepted as the best overall index of kidney function, GFR remains the corner stone of the clinical evaluation of overall kidney function ***(Emilio R, et al. 2007)***.

Over many studies, researchers tried to figure out the most suitable GFR marker regarding accuracy, simplicity, economicity and finally to be expressive to degree of renal damage, our study tries to cope with such precise goal.

Our study was performed to compare between eGFR equations based on serum creatinine and/or cystatin C performance in relation to measured GFR using radionuclide study and degree of proteinuria.

In our cross sectional study, eighty adult type 2 diabetic patients, with overt diabetic nephropathy and proteinuria more than 300 mg/24 hours ,were included after application of inclusion and exclusion criteria, and subjected to history taking, clinical examination and laboratory investigation including serum creatinine, cystatin-C, 24h urinary proteins/creatinine clearance and renal isotopes Tc-DPTA scanning.

Our result showed a linear correlation between serum creatinine and Cystatin c (r=0.867 and P=0.000). Cystatin C was better correlated (r -0.781, p 0.000) with isotopically measured GFR than creatinine (r -0.106, p 0.348). Also the performance of Cystatin C was better than creatinine in all eGFR equation tested in our study

(MDRD, CKD-Epi cr 2009, CKD-Epi cr-Cys 2012, CKD-Epi Cys2012).

The best performance among all equation tested when compared to isotopically measured GFR was the CKD-Epi Cr-Cyst 2012 (r 0.816 p 0.000). Cystatin C showed a significant negative correlation with hemoglobin level a finding which could not established with serum creatinine, there was no significant association of either creatinine or Cystatin with level of proteinuria.

From above mentioned results, we concluded that among patient with early overt diabetic nephropathy, serum Cystatin C showed significant strong correlation better than creatinine with isotopically measured GFR, and among studied equations for GFR estimation, best performance was the CKD-EPI combined creatinine-Cystatin 2012 equation.

- Key words:

(Type 2 diabetes- Diabetic nephropathy-Glomerular filtration rate-Cystatin C- eGFR equations)

INTRODUCTION

Diabetic nephropathy is the single most common disorder leading to kidney failure in adults. In the United States, more than 40% of patients entering end stage renal disease programs are diabetic, most of who (80% or more) have type 2 diabetes. The mortality rate of patients with diabetic nephropathy is high, and a marked increase in cardiovascular risk accounts for more than half of the increased mortality among these patients ***(Michael, et al.2005).***

Once overt diabetic nephropathy, manifesting as proteinuria, is present, ESRD can be postponed (but in most instances not prevented) by effective antihypertensive treatment and careful glycemic control. Thus, in the past 10 to 15 years, there has been intensive research into early predictors of diabetic nephropathy risk, pathophysiologic mechanisms of diabetic kidney injury, and early intervention strategies ***(Michael, et al. 2005).***

GFR prediction is widely employed to screen for chronic kidney disease especially in high-risk groups such as persons with diabetes. Strong evidence supports the need for early detection of diabetic nephropathy, when timely intervention can improve long-term outcome.

Determination of glomerular filtration rate (GFR) by clearance methods or isotopic study is time consuming, troublesome for the patient and costly. Moreover, there is a possibility of inaccuracies associated with these methods especially faulty urine collection.

Therefore, the measurement of endogenous blood substances is used to estimate GFR in the common practice. An ideal marker of GFR is defined as an endogenous substance that, produced at a constant rate is freely disposed of by the kidney only by glomerular filtrations, without being either secreted or reabsorbed by tubular cells.

❖ Cystatin C is a 122 – amino acid, 13 – kDa protein that is a member of the family of (cysteine proteinase inhibitors). It is the product of a “housekeeping” gene expressed in all nucleated cells and is produced at a constant rate. Because of its small size and basic pH (~ 9.0), cystatin C is freely filtered by glomerulus. Cystatin C does not return to the blood stream and is not secreted by renal tubules; it has been suggested to be closer to the “ideal” endogenous marker.

- **Aim of work**

There are no clear data from local Egyptian studies comparing serum cystatin C and serum creatinine levels in type 2 diabetic subjects with overt diabetic nephropathy (proteinuria more than 300mg/24hour).

Hence this study was conducted with the following aims: determine whether serum cystatin C is a better marker of GFR when compared with serum creatinine in Egyptian type 2 diabetic subjects with established diabetic nephropathy and elevated plasma creatinine up to 3 mg/dl.

TYPE 2 DIABETES MELLITUS

Background:

Type 2 diabetes mellitus consists of an array of dysfunctions characterized by hyperglycemia and resulting from the combination of:

- Resistance to insulin action.
- Inadequate insulin secretion.
- Excessive or inappropriate glucagon secretion.

Poorly controlled type 2 diabetes is associated with an array of microvascular, macrovascular, and neuropathic complications.

- Microvascular complications of diabetes include retinal, renal and possibly neuropathic disease.
- Macrovascular complications include coronary artery and peripheral vascular disease.
- Diabetic neuropathy affects autonomic and peripheral nerves.

Diabetes mellitus is a chronic disease that requires long-term medical attention to limit the development of its devastating complications and to manage them when they do occur. It is a disproportionately expensive disease; in the United States in 2007, the direct medical costs of diabetes were $116 billion, and the total costs were $174 billion; people with diabetes had average medical expenditures 2.3 times those of people without diabetes. The emergency department utilization rate by people with diabetes is twice that of the unaffected population. (**U.S. Department of Health and Human Services, CDC, 2011).**

○ Pathophysiology:

Type 2 diabetes is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells. Insulin resistance, which has been attributed to elevated levels of free fatty acids and proinflammatory cytokines in plasma, leads to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased breakdown of fat.

A role for excess glucagon cannot be underestimated; indeed, type 2 diabetes is an islet paracrinopathy in which the reciprocal relationship between the glucagon-secreting alpha cell and the insulin-secreting beta cell is lost, leading to hyperglucagonemia and hence the consequent hyperglycemia. (**Unger RH, et al. 2010)**

For type 2 diabetes mellitus to occur, both insulin resistance and inadequate insulin secretion must exist. For example, all overweight individuals have insulin resistance, but diabetes develops only in those who cannot increase insulin secretion sufficiently to compensate for their insulin resistance. Their insulin concentrations may be high, yet inappropriately low for the level of glycaemia.

With prolonged diabetes, atrophy of the pancreas may occur. A study by **Philippe, et al** used computed tomography (CT) scan findings, glucagon stimulation test results, and fecal elastase-1 measurements to confirm reduced pancreatic volume in individuals with a median 15-year history of diabetes mellitus (range, 5-26 years) **(Philippe MF, et al. 2011).**

This may also explain the associated exocrine deficiency seen in prolonged diabetes.