DOI: 10.31357/fmesmph.2014.00143

SERUM CYSTATIN C AS A MARKER IN THE ASSESSMENT OF RENAL FUNCTION IN PATIENTS WITH RETINOPATHY AND MILD TO MODERATE DIABETIC NEPHROPATHY

By

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Thesis submitted to the University of Sri Jayewardenepura for the award of the degree of Master of Philosophy in Biochemistry on 8th of April 2014.

DECLARATION BY THE CANDIDATE

The work described in this thesis was carried out by me under the supervision of Professor Hemantha Peiris (Chair professor, Department of Biochemistry, Faculty of Medical Sciences, University of Sri Jayewardenepura), Dr. P.P. Rasika Perera (Senior lecturer, Department of Biochemistry, Department of Biochemistry, Faculty of Medical Sciences, University of Sri Jayewardenepura) and Professor.(Mrs.) Kamani Wanigasuriya (Senior Lecturer, Department of Medicine, Faculty of Medical Sciences, University of Sri Jayewardenepura) and a report on this has not been submitted in whole or in part to any University or any other institution for another Degree/Diploma.

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Declaration by the supervisors

We certify that the above statement by the candidate is true and that this thesis is suitable for submission to the University for the purpose of evaluation.

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Dedication

I dedicate this thesis to

my husband, parents,

teachers and very close friends

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Abbreviations

A	
ACEi	Angiotensin converting enzyme inhibitor
ACR	Albumin to creatinine ratio
ADA	American Diabetes Association
AER	Albumin excretion rate
ANOVA	Analysis of Variance
ARB	Angiotensin receptor blockers
AUC	Area under the curve
B	
BMI	Body mass index
C	
CKD	Chronic kidney disease
CG	Cockcroft–Gault equation
^{51}Cr-EDTA	^{51}Cr-ethylenediaminetetra-acetic acid
CVD	Cardiovascular disease
CysC	Serum cystatin C
D	
DR	Diabetic retinopathy
DXA	Dual energy X-ray absorptiometry
E	
eGFR	Estimated glomerular filtration rate

eGFR-MDRD	Estimated glomerular filtration rate based on MDRD equation
eGFR-CKD EPI	Estimated glomerular filtration rate based on CKD EPI equation
eGFR-CysC	Estimated glomerular filtration rate based on serum cystatin C
eGFR-SCr	Estimated glomerular filtration rate based on serum creatinine
ESRD	End stage renal disease
G	
GFR	Glomerular filtration rate
H	
HDL	High density lipoprotein
HSD	Honestly Significant Difference
I	
IFCC	**International Federation of Clinical Chemistry**
K	
KDIGO	Kidney Disease Improving Global Outcomes
L	
LDL	Low density lipoprotein
M	
macroAU	Macroalbuminuria
MAU	Microalbuminuria
mGFR	Measured glomerular filtration rate
N	
NAU	Normoalbuminuria

NHANES III	Third National Health and Nutrition examination Survey
NKDEP	National Kidney Disease Education Program
NICE	National Institutes for Clinical Excellence
NIST	National Institute of Standards and Technology
NPDR	Non proliferative diabetic retinopathy
P	
PENIA	Particle enhanced nephelometric immunoassay
PETIA	Particle enhanced turbidimetric immunoassay
PDR	Proliferative diabetic retinopathy
R	
REGARDS	**Reasons for Geographic and Racial Differences in Stroke**
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
ROC	Receiver operating curves
S	
SCr	Serum creatinine
SD	Standard deviation
SPSS	Statistical Package for Social Sciences
SRM	Standard Reference Material
STDR	Site threatening diabetic retinopathy
T	
T2DM	Type 2 diabetic patients

^{99m}Tc-DTPA	^{99m}Tc-diethylenethiaminepenta -acetic acid

U

UAC	Urine albumin concentration
UAE	Urine albumin excretion
UKPDS	United Kingdom Prospective Diabetes Study

W

WHR	Waist to Hip Ratio

ACKNOWLEDGEMENTS

My deepest gratitude goes to my supervisor, Prof. Hemantha Peiris who introduced me to Cystatin C and motivated me to carry out my research work. His advices, encouragement and guidance are highly appreciated. Also my deepest gratitude is extended to Dr. P.P.Rasika Perera, my second supervisor, who's invaluable, unwavering enthusiasm and mentoring kept me engaged with my research. This thesis would not have been possible without their help, support and patience. I would also like to thank my other supervisor, Prof. Kamani Wanigasuriya, who provided expert advice, guidance and supported me to carry out my research work in the clinical setup.

I'm also grateful for Dr. Uditha Bulugahapitiya, Consultant Endocrinologist and the staff of the Diabetic clinic at Colombo South Teaching hospital and also to Dr. M. Wijesuriya the director and the staff of the National Diabetes Center, Rajagiriya for the support given in recruiting patients. I would also like to thank Dr. Ranjith Kodikara, Consultant Eye surgeon and the staff of the Eye clinic, Colombo South Teaching hospital for the invaluable support extended by carrying out eye examinations of the diabetic patients recruited for the study.

I would like to thank the Director and the staff of Colombo South Hospital, Dr. A.L.P. Seneviratne, Head of Department of Family Medicine, Faculty of Medical Sciences, University of Sri Jayewardenepura and the staff of the Family Practice center at University of Sri Jayewardenepura for all the support given in carrying out my research.

My appreciation also extends to Dr. W.A. Ananda Wijayasiri, Senior lecturer, Department of Community Medicine, Faculty of Medical Sciences, University of Sri Jayewardenepura and Mr. Benoit Ahanda (MSc in Statistics), PhD student, Department of Mathematics and Statistics, Texas Tech University, Lubbock ,Texas for helping me with the statistical analysis.

I also thank the academic and non-academic staff of the Department of Biochemistry, Faculty of Medical Sciences, University of Sri Jayewardenepura for the academic and technical support and assistance since the start of my postgraduate work.

My research would not have been possible without the financial assistance from the University of Sri Jayewardenepura (University grant - ASP/06/R/MED/2011/21) and National Science Foundation, Sri Lanka (Competitive NSF Research grant – RG/2011/HS/21).

I appreciate all the encouragement and support given by my husband, my parents and friends.

Last but not least, my sincere gratitude is extended to all the subjects who participated very willingly in my study.

Serum Cystatin C as a marker in the assessment of renal function in patients with retinopathy and mild to moderate diabetic nephropathy

Nadeeja Niranjalie Wijayatunga

ABSTRACT

Introduction: Serum cystatin C (CysC) has been described as a promising marker of GFR. However there are no literature on performance of CysC in nephropathy and retinopathy (DR), in Sri Lankan type 2 diabetic patients (T2DM).

Objectives: To determine correlation between serum CysC and Serum Creatinine (SCr), Albumin to Creatinine Ratio (ACR), and estimated glomerular filtration rate based on Modification of Diet for Renal Disease study equation (eGFR-MDRD) in both T2DM patients and healthy adults, to compare CysC levels in T2DM subjects with mild to moderate diabetic nephropathy with age and gender matched healthy individuals and also to identify the correlation of DR in those selected T2DM patients with Cys, SCr, eGFR-MDRD and ACR.

Methods: Sixty one T2DM patients with possibility of mild to moderate renal impairment, and 118 apparently healthy adults, between 30-60 years were enrolled. Out of the 118 healthy adults, 61 were age and gender matched with the T2DM patients. Retinopathy status was assessed by slit lamp examination. SCr and CysC and urine creatinine and albumin were measured. ACR and eGFR-MDRD, eGFR- Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) were calculated.

Results: CysC significantly correlated with SCr and eGFR –MDRD in bothT2DM patients and healthy adults but was stronger in the T2DM patients. CysC significantly

correlated with ACR severity categories only in T2DM patients with a significant stepwise increase of CysC according to degree of albuminuria. The T2DM patients (n=61) had higher CysC than the matched controls. Both T2DM patient groups with moderate diabetic nephropathy (n=21) and microalbuminuria (n=22) had higher CysC than the respective matched healthy control groups ($p<0.05$). Only the ACR categories showed a significant correlation with DR categories ($P<0.05$). CysC cut off value for the diagnosis of moderate renal impairment was 0.98mg/L (sensitivity of 85.7%, specificity of 82.5%) and for albuminuria (ACR >30mg/g) was 0.96 mg/L (sensitivity of 73.3% and a specificity of 80.6%). Only CysC could differentiate the moderately increased chronic kidney disease (CKD) risk prognosis category from the absent/low CKD risk category ($p < 0.05$). The reference intervals for the healthy adults for < 50 years of age for male and females are 0.62 – 1.01 mg/L and 0.54 – 0.90 mg/L respectively while for > 50 years of age for males and females are 0.65 – 1.12 mg/L and 0.60 – 1.01 mg/L respectively.

Conclusion: CysC may be used as a reliable renal function marker in T2DM patients with mild to moderate diabetic nephropathy and it is also useful in early detection of poor prognosis in CKD. ACR may be able to predict DR status in T2DM patients. Our study suggests that screening for low GFR with CysC in a low-risk population is probably not worthwhile. In healthy adults, gender based reference intervals for less than 50 year and more than 50 years of age are suggested.