Role of Cystatin C in early detection of renal impairment in Pre-diabetics

Thesis

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List of Abbreviation

Abb.	Full term
1-hrPP	1 hour postprandial
2-hrPP	2 hours postprandial
AACE	American association of clinical endocrinologists
ACE	Angiotensin converting enzyme
ACR	Albumin/creatinine ratio
ADA	American Diabetes Association
AER	Albumin excretion rate
ARBs	Angiotensin II receptor blockers
BM	Basement membrane
BMI	Body mass index
BP	Blood pressure
CABG	Coronary aretery bypass grafting
CAD	Coronary artery disease
CHD	Coronary heart disease
CKD	Chronic kidney disease
CSF	Cerebrospinal fluid
CST3	Cystatin C
CST9	Cystatin 9
CVD	Cardiovascular disease
Cys-C	Cystatin C
DCCT	Diabetes Control and Complications Trial
DECODE	Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe
DKD	Diabetic kidney disease
DN	Diabetic nephropathy
DPP	Diabetes Prevention Program
DPP4 inhibitors	Dipeptidyl peptidase 4 inhibitor
DRIs	Direct renin inhibitors
eGFR	Estimated glomerular filtration rate
EGP	Endogenous glucose production
eNOS	endothelial nitric oxide synthase
ESRD	End Stage Renal Disease

List of Abbreviation (Cont…)

Abb.	Full term
FBG ..... :	Fasting blood glucose
FFA..... :	Free Fatty Acids
GBM ..... :	Glomerular basement membrane
GDM..... :	Gestational diabetes mellitus
GFR ..... :	Glomerular Filtration Rate
GLP-1 ..... :	Glucagon-like peptide-1
GWAS ..... :	Genome-wide association study
HCC..... :	Human cystatin C
HCCAA ..... :	hereditary cystatin C amyloid angiopathy
HDL..... :	High Density Lipoprotein
HGO ..... :	Hepatic glucose output
HOMA..... :	Homeostasis Model Assessment
ICAM-1 ..... :	Intercellular adhesion molecule-1
IDF..... :	International Diabetes Federation
IDNT..... :	International dietetics and nutrition terminology
IFG..... :	Impaired fasting glucose
IGT ..... :	Impaired glucose tolerance
IL-6..... :	Interleukin 6
IR ..... :	Insulin resistance
IRF8..... :	Interferon regulatory factor 8
JAK-STAT ..... :	Janus kinases-signal transducer and activator of transcription signaling
kDa ..... :	kilodalton
KDIGO ..... :	Kidney Disease:Improving Global Outcomes
KORA..... :	Cooperative health research in the region of Augsburg
LDL ..... :	Low density lipoproteins
MAP- kinase..... :	Mitogen-activated protein kinase
MCP-1 ..... :	Monocyte chemoattractant protein-1
MDRD ..... :	Modification of Diet in Renal Disease
MMP-2 ..... :	Matrix metalloproteinase-2

List of Abbreviation (Cont…)

Abb.	Full term
NADPH ..... :	Nicotinamide adenine dinucleotide phosphate oxidase
NDDG..... :	National Diabetes Data Group
NF-kB ..... :	Nuclear factor Kappa-light-chain-enhancer of activated Bcells
NGT ..... :	Normal glucose tolerance
NHANES..... :	National Health and Nutrition Examination Survey
NO ..... :	Nitric oxide
OGTT ..... :	Oral glucose tolerance test
PAI-1 ..... :	Plasminogen activator inhibitor-1
PCI..... :	Percutaneous coronary intervention
PI 3-kinase..... :	Phosphatidylinositol 3-kinase
PK C ..... :	Protein kinase
PPAR-γ ..... :	Peroxisome proliferator-activated receptor gamma
PU.1 ..... :	The macrophage transcription factor
RAS ..... :	Renin angiotensin system
RENAAL..... :	Reduction in endpoints with angiotensin antagonist losartan
ROS ..... :	Reactive oxygen species
RR..... :	Relative risk
sCr..... :	Serum creatinine
SGLT2 ..... :	Sodium-glucose co-transporter 2
SHARP ..... :	The Study of Heart and Renal Protection
SNPs ..... :	Single-nucleotide polymorphisms
T2DM ..... :	Type 2 Diabetes Mellitus
TBM ..... :	Tubular basement membrane
TG..... :	Triglycerides
TGF ..... :	Transforming growth factor
TNF ..... :	Tumor necrosis factor
UAE..... :	Urinary albumin excretion
UKPDS..... :	The United Kingdom prospective diabetes study
VCAM 1 ..... :	Vascular cell adhesion molecule 1
VEGF..... :	Vascular endothelial growth factor
VLDL ..... :	Very low density lipoprotein
WHO..... :	World Health Organization

INTRODUCTION

Pre-diabetes is an asymptomatic condition not associated with functional impairment that mostly presents prior to the individual developing type 2 diabetes ***(De vegt et al., 2001)***. It consists of impaired fasting glucose (IFG) (100-125 mg/dl), impaired glucose tolerance (IGT) (140-199 mg/dl), or both ***(Genuth et al., 2008).***

5-10 % of people per year with pre-diabetes will progress to diabetes, with the same proportion converting back to normoglycaemia. Prevalence of pre-diabetes is increasing worldwide and experts have projected that more than 470 million people will have pre-diabetes by 2030. pre-diabetes is associated with the simultaneous presence of insulin resistance and beta cell dysfunction-abnormalities that start before glucose changes are detectable ***(Tabák et al., 2012).***

Risk factors for developing diabetes mellitus include: age; ethnicity; weight; first-degree relative with type 2 diabetes; low birthweight and sedentary lifestyle. Certain comorbidities increase the risk of type 2 diabetes, these include: cardiovascular and cerebrovascular disease; polycystic ovary syndrome; a history of gestational diabetes; and mental health problems ***(Savill, 2012).***

Cystatin C, a cyteine protease inhibitors freely filtered by the renal glomeruli, metabolised by the proximal tubule, has been identified as an early marker of renal failure. Cystatin C is produced at a constant rate by nucleated cells and released into the bloodstream with a half-life of about 2 hours. Its concentration is almost totally dependent on the glomerular filtration rate ***(Willems et al., 2009)*.**

Cystatin C may detect mild-to-moderate decreases in GFR that are not evident with serum creatinine-based measurements. Some studies suggest that CysC–GFR was better than creatinine-based estimates of GFR at GFR levels >60 mL/min/1.73 m2 (CKD stages 1 and 2). In addition, CysC–GFR appeared to be better correlated with microalbuminuria, while MDRD and CG creatinine estimates of GFR tend to reflect only proteinuria ***(Yang et al., 2007)*.**

AIM OF THE WORK

The aim is to study the role of Cystatin C in early detection of renal affection in the pre-diabetics.

PREDIABETES

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Cutoff glycemic levels defining diabetes are based on the observed association between certain glucose levels and a dramatic increase in the prevalence of microvascular complications considered specific for hyperglycemia (retinopathy and nephropathy) ***(Martin and Michael, 2011)***.

In 1979, the National Diabetes Data Group (NDDG) first introduced the concept of a metabolic state intermediate between normal glucose homeostasis and diabetes, called glucose intolerance. Individuals with glucose intolerance did not meet the criteria for being diagnosed with diabetes but had glucose levels higher than those considered normal ***(Diabetes Prevention Program Research Group, 2007).***

Although Type 2 diabetes is a globally growing public health concern, a much larger segment of the world's population is actually diagnosed with pre diabetes, which is defined as having blood glucose concentrations higher than normal, and not yet meeting the definition of diabetes per se. Based on the World Health Organization (WHO), individuals with pre-diabetes have impaired fasting glucose concentration (IFG) ranging between 110 mg/dl and 126 mg/dl, and/or impaired glucose tolerance (IGT), defined as plasma glucose

concentration 2 h post 75 g oral glucose load, ranging between 140 mg/dl and 199 mg/dl ***(World Health Organization, 2006)***.

The American Diabetes Association (ADA), uses the same WHO definition for the post-load threshold values for impaired glucose tolerance however a lower cutoff value for impaired fasting glucose is used and it ranges between100 and 125 mg/dl. Furthermore, the ADA stated that glycated hemoglobin (HbA1c) between 5.7 and 6.4% can also be used for diagnosing pre diabetes. It is important to note that the ADA and the WHO recognize that HbA1c level ≥6.5% is indicative of diabetes ***(American Diabetes Association, 2013).***

Progression from prediabetes to diabetes:

"Prediabetes" is the term used for individuals with IFG and/or IGT, indicating the relatively high risk for the future development of diabetes. IFG and IGT should not be viewed as clinical entities in their own right but rather risk factors for diabetes and cardiovascular disease (CVD). IFG and IGT are associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension ***(American Diabetes Association, 2014).***

As per the International Diabetes Federation, 382 million people worldwide, or 8.3% of adults, were found to have diabetes in the year 2013 and by the year 2035 this will rise to