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Relation between Pre-Procedural Increase in Urinary Albumin Excretion and Changes in Estimated Glomerular Filtration Rate after Coronary Angiography in Diabetic Patients

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالُوا

سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

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List of Abbreviations

ACE	angiotensin-converting enzyme
ACR	albumin/creatinine ratio
AER	albumin excretion rates
AKI	acute kidney injury
ARBs	angiotensin II receptor blockers
ATN	acute tubular necrosis
CIN	Contrast-induced nephropathy
CKD	chronic kidney disease
CLI	critical limb ischemia
CM	contrast medium
CT	computed tomography
DCCT	Diabetes Control and Complications Trial
DN	Diabetic nephropathy
DN	diabetic nephropathy
eGFR	estimated glomerular filtration rate
ESRD	End stage renal disease
FENa	fractional sodium excretion
FUs	foot ulcers
GFR	glomerular filtration rate
ISPAD	International Society of Pediatric and Adolescent Diabetes
LOCM	low-osmolar contrast media
MDRD	Modification of Diet in Renal Disease
NO	Nitric oxide

NSAIDs	Nonsteroidal anti-inflammatory drugs
RBCs	Red blood cells
ROC	Receiver operating characteristic
ROS	Reactive oxygen species
SPSS	Statistical Package for Social Sciences
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
UKPDS	United Kingdom Prospective Diabetes Study
WBCs	white blood cells

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ABSTRACT

Background: Contrast-induced nephropathy (CIN), is an acute impairment in renalfunction, and typically occurs within 3 days following the exposure to a contrast medium (CM). It is associated with increased hospital stay and increased morbidity and mortality, Adult patients with diabetes have a higher risk than the general population for developing contrast induced nephropathy.

Methods : The current study includes 40 patients with diabetes mellitus, scheduled for coronary angiography with estimated GFR >60 ml/min .the patients were divided according to their pre-procedural urinary albumin creatinine ratio (ACR) results into 3 groups: Group 1 included patients with pre-procedure urinary albumin creatinine ratio < 30mg/g , Group 2 included patients with pre- procedure albumin creatinine ratio 30- 300 mg/g and Group 3 included patients with pre-procedure albumin creatinine ratio >300 mg/g . Estimated GFR (glomerular filtration rate) calculated using MDRD and serum creatinine were measured at day 2 and 3 (Day +2 +3) after coronary angiography.

Results: There was no statistically significant difference in the age and gender distribution, the use of ACEIs (angiotension converting enzyme inhibitors) or diuretics between the cases who developed and who didn't develop CIN. The mean ACR in the group with no contrast induced nephropathy was 225.38 ± 209.53 which was statistically significantly lower when compared with the cases with contrast induced nephropathy (420.43± 348.52) (p=0.033). The mean HbA1c in no contrast induced nephropathy group was 7.11 ± 0.64 and in contrast induced nephropathy group it was 9.09 ± 0.66 which is significantly higher (P>0.001).With univariate regression analysis, ACR, HbA1c and number of vessels affected were shown to be risk factors for occurrence of CIN after use of contrast, but with multivariate analysis, both ACR and HbA1c were shown to be risk factors for CIN.

Conclusion: An increase in albumin creatinine ratio in itself can be a risk factor for
development of contrast induced nephropathy in diabetic patients**.**

Keywords: Diabetes, proteinuria, contrast induced nephropathy, coronary angiography, acute kidney injury

Introduction

Cardiovascular imaging modalities with the use of contrast medium have been expanded worldwide in the clinical setting. Of those, coronary computed tomography angiography (CCTA) is a contemporary, convenient examination and has been commonly applied for detecting significant coronary atherosclerosis in patients with a low likelihood but suspected coronary artery disease because of an extremely high negative predictive value *(Nørgaard et al., 2014)*.

However, any repetitive use of CCTA must be approached with special caution because this examination calls for the use of a relatively high dose of iodine-containing contrast media. This examination is contraindicated for subjects with overt kidney dysfunction is necessary *(Isobe et al., 2017)*.

In addition, some patients are required to undergo subsequent diagnostic coronary angiography and/or therapeutic coronary angioplasty, eventually being concerned about additional exposure to contrast medium. Thus, the early detection of patients who are prone to show post-procedural renal functional deterioration prior to this examination *(Stacul et al., 2011)*.

The number of diabetic patients is expected to increase exponentially and the onset is occurring at even younger ages. Because atherosclerotic cardiovascular dis-eases often coexist in diabetic patients, coronary evaluations with the use of contrast media are mandatory in diabetic patients with suspected coronary artery disease. Diabetes is also one of the risks for development of CIN *(Stolker et al., 2010; Naruse et al., 2012)*.

In addition, diabetic patients often have the presence of urinary microalbumin, which is a potential marker of subclinical renal dysfunction and associated with future diabetic nephropathy *(Pakfetrat et al., 2010)*.

However, the use of coronary angiography must be approached with special caution because this examination calls for the use of a relatively high dose of iodine-containing contrast media. This examination is contraindicated for subjects with overt kidney dysfunction. Thus, the early detection of patients who are prone to show post-procedural renal functional deterioration prior to this examination using reliable renal markers is crucial.

Aim of the work

The aim of this study is to investigate the value of pre-procedural measurement of albumin excretion ratio on renal functional changes after coronary angiography in diabetic patients.

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Chapter One: Diabetic Nephropathy

Diabetic nephropathy (DN) is a syndrome manifested by presence of persistent pathological proteinuria , glomerular damage , and decrease of glomerular filtration rate (GFR) in diabetic patients *(Lim, 2014)*.

Epidemiology

In the United Kingdom, 10 years following diagnosis of diabetes, the prevalence of microalbuminuria was 24.9%, of macroalbuminuria was 5.3%, and of elevated plasma creatinine or renal replacement therapy was 0.8%. Patients with elevated plasma creatinine or renal replacement therapy had an annual death rate of 19.2% *(Reutens and Atkins, 2011)*.

The prevalence of microalbuminuria was about 14% in group of diabetic patients aged less than 18 and with innless duration more than 5 years, as reported in EURODIAB ACE study. Moreover, about 80% of male and 50% of female patients had developed proteinuria (micro or macroalbuminuric range) with increase duration of diabetes more than 30years *(De Boer et al., 2011)*.

Etiology

Hyperglycemia

Hyperglycemia causes renal injury and hyperfiltration as advanced glycation products, cause activation of cytokines and initiation of inflammation process that leads to structural changes in basement membrane and mesangial cells. Protein kinase C, which (cause renal disease and other vascular complications of diabetes) is activated by hyperglycemia *(Singh et al., 2014)*.

Glycemic control defined as the equivalent between dietary intake and gluconeogenesis and tissue uptake or utilization through storage as glycogen or fat and oxidation *(Odegaard and Chawla, 2012)*.

Role of immunity

Many researches have focused on the vital function of innate immunity and regulatory T-cells because of autoimmune nature of diabetes with overlapping pathophysiology of both type 1 and type 2 DM *(Odegaard and Chawla, 2012)*.

Genes

Certain ethnic groups, especially African Americans and American Indians, were highly susceptible to nephropathy and other microvascular complications of diabetes regardless of other risk factors. This is due to highly genetic susceptibility of these races *(Association, 2017)*.

Moreover a polymorphism in the gene for angiotensin-converting enzyme (ACE) had a role in developing or progression of nephropathy. so the epigenetic modification on nephropathy must be highlighted *(Deshpande et al., 2013)*.

Folic acid

The correlation between decrease in serum folic acid levels and diabetic nephropathy was studied in 100 type 2 diabetic patients. Statistical analysis showed that decreased folic acid levels elevate the risk of diabetic nephropathy by 19.9% *(Bherwani et al., 2016)*.

Pathophysiology

The pathophysiology leading to the development of diabetic nephropathy and resultant end-stage kidney disease follows from the diabetic milieu leading to the generation and circulation of advanced glycation end products, elaboration of growth factors, and hemodynamic and hormonal changes. These lead to the release of reactive oxygen species and inflammatory mediators. Collectively, these changes result in glomerular hyperfiltration, glomerular hypertension, renal hypertrophy, and altered glomerular composition, which is manifested clinically as albuminuria and hypertension. Pathologically, the kidneys undergo several changes, including deposition (in primarily the mesangium) of extracellular matrix, glomerular basement membrane thickening, proliferative changes, and tubular atrophy, ultimately resulting in interstitial fibrosis and glomerulosclerosis (the final common pathway of many kidney diseases). *(Kashihara et al., 2010; Najafian et al., 2011)*
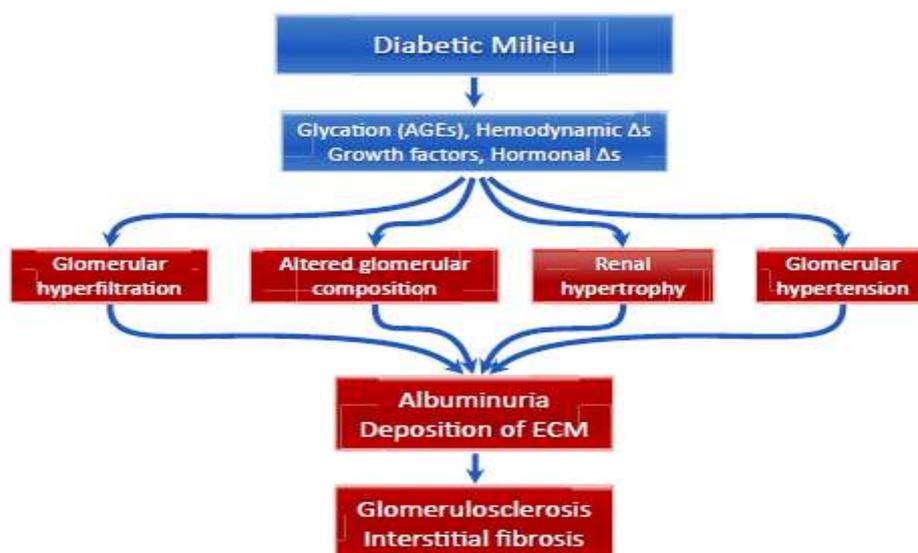

Figure (1): Pathophysiology of diabetic nephropathy. Abbreviations: AGE, advanced glycation end product; ECM, extracellular matrix *(Umanath and Lewis, 2018)*.