EFFECT OF RENAL TRANSPLANTATION ON ADRENOMEDULLIN LEVELS IN DIABETIC CHRONIC KIDNEY DISEASE PATIENTS

Thesis

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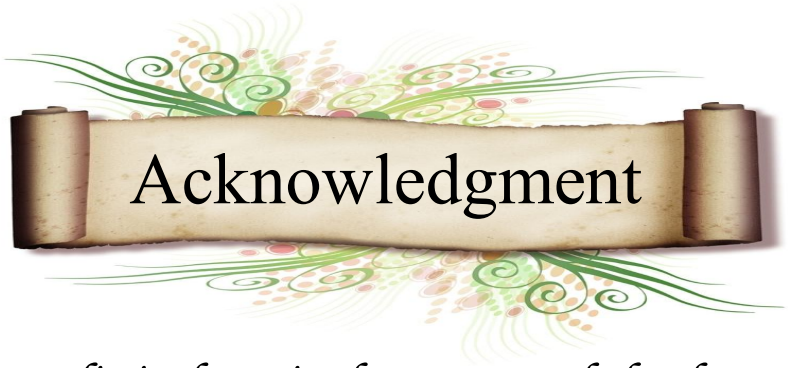

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Abstract

Other studies will be useful to determine whether adrenomedullin infusion might improve renal dysfunction, as it has been shown to be beneficial after myocardial infraction.Further studies are needed to compare mAM and other humoral factors as predictive factors of mortality and morbidity in transplant patients.Further studies are necessary to clarify the pathophysiologic role of mAM in transplant patients complicated with various cardiovascular diseases (peripheral artery disease, stroke, heart failure, etc.) especially the diabetics who are most liable for these complications.

Keyword

ALT- HbA1C- LPS- TNF-α

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List of Abbreviations

iAMD : Adrenomedullin-2, intermedin
ACEI : Angiotensin-converting enzyme inhibitors
ADM : Adrenomedullin
AII : Angiotensin II
ALT : Alanine transaminase
AMBP : Adrenomedullin binding protein
ANP : Atrial natriuretic peptide
AP-2 : Activator Protein-2
AR : Acute Rejection
AST : Aspartate transaminase
BMI : Body Mass Index
BNP : Brain natriuretic peptide
CD : Cluster of Differentiation
CGRP : Calcitonin gene-related peptide
CHF : Congestive heart failure
CRLR : Calcitonin Receptor Like Receptor
DGF : Delayed Graft Function
DM : Diabetes Mellitus
EDTA : Ethylene Diamine TetraAcetate
EGF : Epidermal Growth Factor
EF : Ejection fraction
ELISA : Enzyme Linked Immunosorbant Assay
ESRD : End Stage Renal Disease
ET-1 : Endothelin-1
FS : Fractional shorting
Hb : Hemoglobin
HbA1C : Glycoslated HB
HF : Heart failure
HLA : Human Leucocyte Antigen
HR : Heart rate
IF/TA : Interstial Fibrosis/Tubular Atrophy

LIST OF ABBREVIATIONS *(CONT...)*

LPS : Lipopolysaccharide
LVEDD : Left ventricular end diastolic dimentions
LVESD : Left ventricular end systolic dimentions
MAP : Mean Arterial Pressure
MICA : MHC- class1 related A chain
NEP : Neutral endopeptidase
NIH : National Institute of Health
NO : Nitric oxide
NYHA : New York Heart Association
PAMP : Pro-adrenomedullin N-terminal 20 peptide
PAP : Pulmonary artery pressure
PKC : Proein Kinase C
ROC : Receiver Operating Charachteristic curves
RTx : Renal Transplantation
TGF : Transforming Growth Factor
TNF-α : Tumer necrosis factor
VIP : Vasoactive Intestinal Peptide
VSMC : Vascular smooth muscle cell

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INTRODUCTION

Since the 1950s, kidney disease has been clearly recognized as a common complication of diabetes mellitus (DM), with as many as 50% of patients with DM of more than 20 years duration having this complication. The risk for the development of diabetic nephropathy is low in a normo-albuminuric patient with diabetes' duration of greater than 30 years. Patients who have no proteinuria after 20-25 years have a risk of developing overt renal disease of only approximately 1% per year ***(Pavkov et al., 2006).*** Diabetes itself, remains one of the most common causes of ESRD.

As for any other patient with ESRD, diabetic patients with ESRD can be offered renal replacement therapy usually in the form of haemodialysis. In patients with diabetic nephropathy, starting at a creatinine clearance or estimated GFR of 15 mL/min is wise. Starting earlier may be useful when hypervolemia renders blood pressure uncontrollable, when the patient experiences anorexia and cachexia or other uremic symptoms, and when severe vomiting is the combined result of uremia and gastroparesis. Amongst the options of RRT is renal transplantation (eg, cadaver donor kidney, living related-donor kidney, living unrelated-donor kidney [emotionally related donor], living unrelated-donor kidney [unrelated by family or emotionally; the so-called altruistic donor], pancreas plus kidney transplantation ***(Shlipak, 2009).*** Transplantation offers an excellent option for restoring a healthy productive life besides reducing the overall medical care costs on the long-run. This has attracted researchers to focus on all possible means to improve the outcome of such procedure and limit any possible complications which would certainly benefit both the patient and his society. This opened the door for biomarkers.

A new era has emerged in the medical field with the use of biomarkers as diagnostic and therapeutic agents of various medical diseases. Due to limitations of currently used kidney function markers ***(Iliadis et al., 2011)***, there has been extensive study of biomarkers as traceable substances which are objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention ***(Deverajan, 2007).***

Of these, adrenomedullin is a newly emerging biomarker expected to have a role in the patho-phsiology of renal haemodynamics in the native kidney and non-the-less the transplanted kidney too. It is suggested that adrenomedullin may play an important role in the regulation of systemic vascular tone, control of cardiorenal homeostasis and may influence the cardiovascular dysfunction ***(Yamagushi et al., 1996)***.

In the following pages of this study, we made an effort to highlight the effect of renal transplantation on the levels of adrenomedullin in diabetic renal patients and the possibility of using it as a biomarker in the detection of early rejection.

AIM OF THE WORK

1- To assess the effect of renal transplantation on adrenomedullin levels in the first postoperative week.

2- To highlight the potential effect of diabetes on adrenomedullin levels.

3- Raise the hypothetic role of adrenomedullin in the pathophysiology of diabetes and renal failure.

Biomarkers in Renal Transplantation

In kidney transplantation, significant improvements in short-term allograft survival have been accomplished

However, despite improvement over the years in immuno-suppressant strategies, late kidney allograft loss remains the main clinical challenge for long-term graft survival with close to 5000 kidney transplants failing each year in the USA alone. Kidney transplant failure is now a leading cause of end-stage renal disease ***(Hariharan et al., 2000).***

Thus, there is a critical need for new effective biomarkers for accurate monitoring of graft function, early diagnosis of rejection, treatment response, and surrogate end point and outcome prediction in organ transplantation, leading to a tailored and individualized treatment ***(Meier-Kriesche et al., 2004)*** to improve outcomes in a noninvasive, cost-effective manner.

Recently, a NIH working group recommended preferred terms and definitions that have broad applications ***(Biomarkers Definition Working Group, 2001).***

- Biological marker (biomarker): a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
- Clinical end point: a characteristic or variable that reflects how a patient feels or functions, or how long a patient survives.
- Surrogate end point: a biomarker intended to substitute a clinical end point. A clinical investigator uses epidemiologic,

therapeutic, pathophysiologic or other scientific evidence to select a surrogate end point that is expected to predict clinical benefit, harm or lack of benefit or harm.

The introduction of molecular medicine has resulted in an amazing increase in the discovery of new biomarkers. Much of this is related to the advances in new technologies such as genomics, proteomics and imaging. Furthermore, the expansions in technologies and innovative applications towards translational medicine have driven biomarkers into the focus of drug discovery and development in recent years. However, there is still no routine application of any of these markers in clinical transplantation.

The Human Genome Project and Genomic Sciences resulted in valuable insights into the mechanisms of the genome and have produced a large quantity of tools ***(Cunningham, 2000).*** These tools are enabling a detailed analysis of the expression of the complete set of genes encoded in the genome and are collectively referred to as the 'omics' technologies. The knowledge base being developed by the genomics revolution, through its associated technologies, is impacting on the practice of all of the biological sciences.

Major obstacles in the management of transplant recipients include:

- Most accessible methods for evaluating kidney function are either ineffective, inaccurate or highly invasive, such as tissue biopsies.
- Lack of reliable markers useful for immune monitoring or predicting long-term graft function. in the clinical routine. This is partly due to the lack of well-defined end points and short follow-up times in validation studies. Furthermore, it reflects the absence of robust metrics and a reliance on 'subjective' measures.