ROLE OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS IN TYPE I DIABETIC NEPHROPATHY

DR. NASIM MUSA
Type I –IDDM is characterized by

- The abrupt onset of symptoms
- Insulinopenia
- Dependence on injected insulin for life
- Proneness to ketoacidosis.
- Confirmed by demonstrating low plasma insulin or C-peptide levels, circulating islet cell antibodies and association with HLA DR3, DR4
- Asparagines for neutral amino acids in position 57 of HLA-DQB chain.
### Clinical distinction between type I and type II Diabetes

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>IN FAVOUR OF TYPE I</th>
<th>IN FAVOUR OF TYPE II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis of diabetes</td>
<td>&lt;25 yrs</td>
<td>&gt;40 yrs</td>
</tr>
<tr>
<td>Weight at diagnosis</td>
<td>105% of ideal weight</td>
<td>&gt;115%</td>
</tr>
<tr>
<td>Ketoacidosis within 2 yrs of following diagnosis</td>
<td>++</td>
<td>- -</td>
</tr>
<tr>
<td>Long term complications at diagnosis</td>
<td>- -</td>
<td>+ +</td>
</tr>
<tr>
<td>Delay between diagnosis and insulin deficiency</td>
<td>- -</td>
<td>+ +</td>
</tr>
<tr>
<td>C-peptide</td>
<td>- -</td>
<td>+ +</td>
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</table>
Diabetic nephropathy

- A major micro vascular complication of diabetes mellitus.
- Major cause of morbidity and mortality in both type I and type II diabetes.
- Represent the major cause of ESRD worldwide.
- About 20-40% of all diabetic subjects develop DN.
- Diabetic nephropathy represents a continuum from microalbuminuria to macroalbuminuria and finally ESRD.
- There is vital need to identify and target novel pathophysiological pathways to reduce the rising burden of this disease.
A GRAPH SHOWING RELATIONSHIP BETWEEN KIDNEY FUNCTION, PROTEIN LEAK, AND YEARS OF DIABETES
EPIDEMIOLOGY OF DN-

40% OF TYPE I AND 20% OF TYPE II DIABETICS DEVELOP CLINICALLY SIGNIFICANT NEPHROPATHY.

ACCORDING TO Krolewski et al. PATIENTS WITH IDDM HAVE 30% - 50% RISK OF DEVELOPING DIABETIC NEPHROPATHY OVER 40 YEAR OF DISEASE.

Natural course of renal disease in Diabetes

Time (yrs)

0 5 11-13 13-25 15-27

Onset of Diabetes

Functional Changes
- Increased GFR
- Reversible albuminuria
  - "Normal" BP

Structural Changes
- Increasing GBM thickness
- Nephromegaly

11-13
- Hyperfiltration
- Persistent MA

13-25
- Decreasing GFR
- Overt Albuminuria

15-27
- Normal BP
- Hypertension
- Glomerulosclerosis

End stage Kidney disease

Normoalbuminuria
Incipient Nephropathy - microalbuminuria
Overnephropathy - macroalbuminuria
PATHOPHYSIOLOGY OF DIABETIC NEPHROPATHY

TGF-β → High glucose → Glycation → ROS → ANG II → Mechanical stretch → Podocyte

Mesangium → Type II receptor ↑ → Integrons ↓ → VEGF ↑ → ANG II ↑ → HSPG ↓

Podocyte → GBM Thickening → Apoptosis/detachment

Proteinuria → Tubulointerstitial fibrosis → Renal insufficiency

Source: Diabetes © 2005 American Diabetes Association, Inc.
## STAGES OF DIABETIC NEPHROPATHY

<table>
<thead>
<tr>
<th>STAGE</th>
<th>GLOMERULAR FILTRATION</th>
<th>ALBUMIN</th>
<th>BP</th>
<th>TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>RENAL HYPERFUNCTION</td>
<td>ELEVATED</td>
<td>ABSENT</td>
<td>NORMAL</td>
<td>AT DIAGNOSIS</td>
</tr>
<tr>
<td>CLINICAL LATENCY</td>
<td>HIGH NORMAL</td>
<td>ABSENT</td>
<td>WITHIN OR ABOVE NORMAL</td>
<td>5-15 YRS</td>
</tr>
<tr>
<td>MICROALBUMINuria</td>
<td>NORMAL</td>
<td>20-200ug/min</td>
<td>INCREASED</td>
<td>10-15 YRS</td>
</tr>
<tr>
<td>MICROALBUMINuria OR PERSISTING PROTEINuria</td>
<td>DECREASING</td>
<td>200ug/min</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RENAL FAILURE</td>
<td>DIMINISHED</td>
<td>massive</td>
<td>INCREASED</td>
<td>15-30 YRS</td>
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</table>
MANAGEMENT-

SLOWING THE PROGRESSION OF DN INCLUDES

- OPTIMISING GLYCAEMIC CONTROL
- CONTROL OF HYPERTENSION
- USING ACEI AND/OR ARB.
MANAGEMENT-

- Medicines that are used to treat diabetic nephropathy are also used to control blood pressure.

ACEI such as captopril, lisinopril, ramipril, and enapril, have been shown to protect the kidney function in people with type 1 diabetes.
MANAGEMENT

- ARBS, SUCH AS Candesartan, Irbesartan, Osartan Potassium, may be given with ACEI to provide greater protection of the kidney.

Chavers, BM, Billus, N. Eng J Med 1989; 320:966
ROLE OF ACEI

- ACEI Blocks The Conversion of Angiotensin I To Angiotensin II. They Lower Arteriolar Resistant And Increased Venous Capacity, Increased Cardiac Output And Lower Renovascular Resistance.
- First Orally Active ACEI Was Captopril Which Was Discovered In 1975
ROLE OFARB

- THEY BLOCK THE ACTIVATION OF ANGIOTENSIN II AT AT1 RECEPTORS. BLOCKADE CAUSES VASODILATATION, REDUCES SECRETION OF VASOPRESSIN, REDUCES PRODUCTION OF AND SECRETION OF ALDOSTERONE.

- FIRST ORALLY ACTIVE ARB WAS LOSARTAN WHICH WAS DISCOVERED IN 1980.
ANGIOTENSIN II PLAYS A CENTRAL ROLE IN ORGAN DAMAGE

- AII
  - AT1 Receptor
  - Atherosclerosis
  - Vasoconstriction
  - Vascular hypertrophy
  - LV hypertrophy
  - Fibrosis
  - Remodeling
  - Apoptosis
  - GFR ↓
  - Proteinuria ↑
  - Aldosterone release
  - Glomerular sclerosis

- Stroke
- Hypertension
- Heart failure
- MI
- Renal failure
- Death

*preclinical data
LV = left ventricular; MI = myocardial infarction; GFR = glomerular filtration rate
RENIN-ANGIOTENSIN CASCADE

- Angiotensinogen
  - Non-renin (eg tPA)
- Non-ACE (eg chymase)
- Angiotensin I
- Angiotensin II
- AT₁
- AT₂
- AT₃
- Renin
- ACE
- Bradykinin
- Inactive peptides

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WHAT ARE THE EVIDENCES?

Are The Inhibitors Of Renin- Angiotensin System(ACEIs or ARBs) Really Effective?
ACE-I Is More Renoprotective Than Conventional Therapy In Type I Diabetes

ACE-I Is More Renoprotective Than Conventional Therapy In Type I Diabetes

Micro Hope Study (n=3577)

24% greater decrease in progression to overt Nephropathy in the Ramipril group than placebo
Renoprotective Effect Of Losartan In Diabetic Nephropathy (RENAAL Study, n=1513)

Comparison Of Losartan, Enalapril & Placebo On Microalbuminuria
<table>
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<tr>
<th>STUDY</th>
<th>STUDY DESIGN</th>
<th>SAMPLE SIZE</th>
<th>EXPOSURE</th>
<th>RESULTS</th>
<th>CONCLUSION</th>
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<td>Jacobsen et al</td>
<td>RCT Crossover Design.</td>
<td>20</td>
<td>ACEI &amp;/or ARB.</td>
<td>Treatment with benazepril, valsartan or dual blockade significantly reduce albuminuria and BP compared with placebo. Dual blockade induced an additional reduction in albuminuria of 43% (29 to 54%) compared with any type of monotherapy.</td>
<td>Dual blockade of the RAS may offer additional renal and cardiovascular protection in type I diabetic patients with DN</td>
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<td>RCT Multi-center Parallel design.</td>
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<td>ACEI &amp; ARB.</td>
<td>Change in mesangial fractional volume per glomerulus over 5-year period did not differ significantly between Placebo(0.016 units) and Enalapril(0.005, p=0.38) or Losartan group</td>
<td>Early blockade of the renin-angiotensin system in patients with type I diabetes did not slow nephropathy progression.</td>
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<td>ACEI.</td>
<td>Total 65 patients reached endpoint, of which 23 were in captopril group and 42 were in placebo group. Treatment with captopril is associated with 50% reduction of in risk of combined end points of death. Dialysis or renal transplantation.</td>
<td>Captopril protect against deterioration of renal function in IDDM Nephropathy irrespective of BP status. The therapy is effective on patient with established nephropathy rather not as prophylactic treatment.</td>
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<td>Increase in GFR was seen 14% by the add-on Losartan therapy and fall of Plasma rennin activity by 32%.</td>
<td>Add on Losartan therapy didn’t improve proteinuria or ABP over one month add on therapy.</td>
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<td>Schjoedt et al</td>
<td>Clinical audit. Follow-up Study.</td>
<td>227</td>
<td>ACEI or ARB.</td>
<td>With RAS blockade mean decline in UAER of 4% year. 65 patients(29%) progressed to overt Diabetic Nephropathy, about 3.1%/yrs. 29 of them regressed to normo-or microalbuminuria on intensified antihypertensive treatment.</td>
<td>Implementation of RAAS-blocking treatment in type I diabetic patients with microalbuminuria successfully reduced long-term progression to overt Diabetic Nephropathy.</td>
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<td>Tarnow et al</td>
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<td>ACEI vs Ca antagonist.</td>
<td>GFR declined in a biphasic manner with an initial(0-6months) reduction of 1.3+_0.3ml_min^-1_month^-1 in the lisinopril group compared with0.2+_0.4ml_min^-1_month^-1 in the nisoldipine group (p_0.01).</td>
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<td>N=</td>
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CONCLUSION-

FURTHER STUDIES AS WELL AS REVIEW WITH HOMOGENEOUS SUBJECT EXPSURE AND OUTCOME COULD UNVEIL DEFINITIVE EVIDENCE REGARDING ROLE OF ACEI AND ARB FOR PREVENTION AS WELL AS FOR TREATMENT OF DIABETIC NEPHROPATHY IN IDDM PATIENT.
THANK YOU