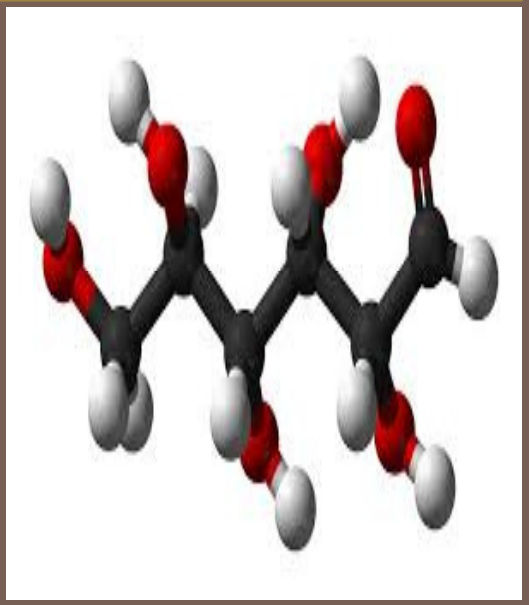
CONTROL OF DELTA(D) GLUCOSE WITH INTENSIVE INSULIN THERAPY IS FUNDAMENTAL TO RENAL PRESERVATION IN DIABETES



By Anil K. Mandal, MB, BS,
Fulbright Scholar
Consultant in Nephrology
Courtesy Clinical Professor of Medicine,
University of Florida, Gainesville, Florida
Adjunct Professor of Pathology and
Laboratory Medicine, University of North
Carolina at Chapel Hill, USA

Mandal Diabetes Research Foundation
tax-exempt charitable organization
St. Augustine, Florida, USA



[1]

Endocrinology 2014
Chicago, Illinois
October 20-21, 2014

Background
Provocative Factors

- 1. Evidence-based vs Observational Studies
- 2. Prevailing commercialism in Diabetes Care is the Road to Diabetic Complications
- 3. High Incidence of Acute Renal Failure associated with use of Angiotensin Converting Enzymes (ACEI) and or Angiotensin Receptor Blocker (ARB)
- 4.High incidence of End Stage Renal Disease (ESRD) and Dialysis as per above.

2. Prevailing Commercialism in Diabetes Care is the Road to Diabetes Complications

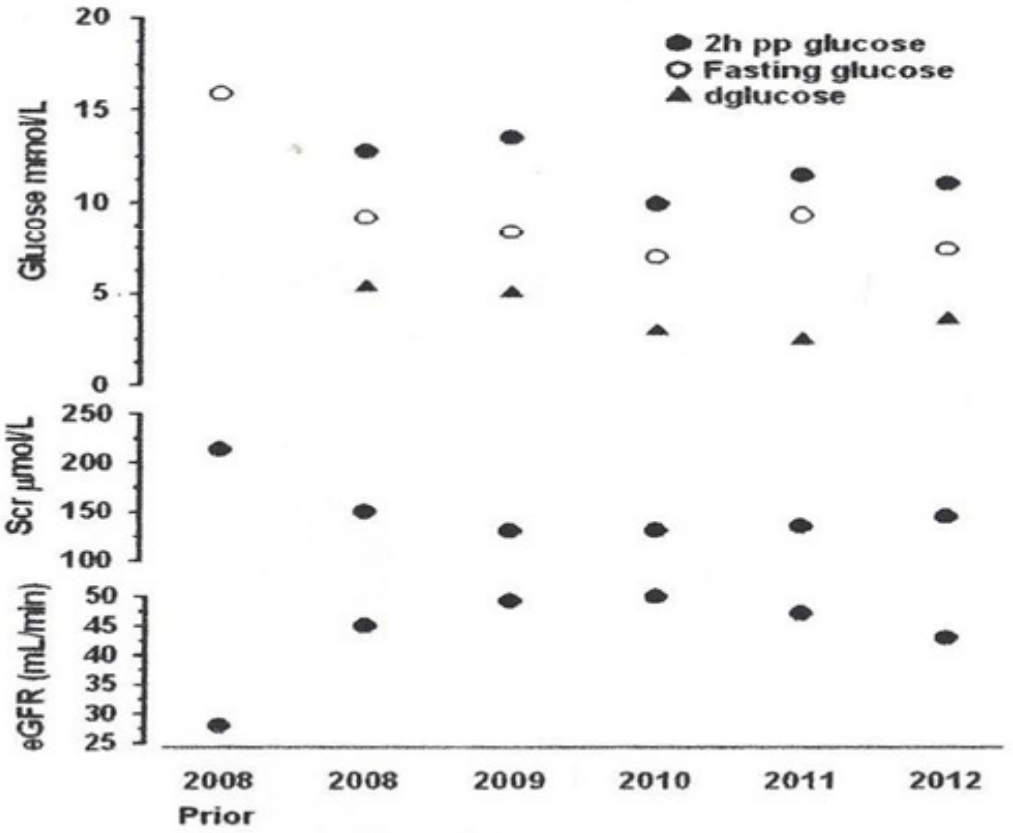
- 1. Adult with elevated blood glucose or HbA1c receives automatic diagnosis of Type 2 diabetes
- 2. **Automatic Prescription** follows for:
  - 1. Metformin 500 mg P.O. BID
  - 2. ACEI/ARB: Lisinopril, Enalapril or Losartan
  - 3. HbA1c in 3 months

Let us examine the consequence of these "Bird like" actions

Answers Follows

4

A 75 year old white male went to a urologist's office for difficulty in urination. Diabetes was detected and treated with Glucotrol XL 10mg PO daily, metformin 500mg PO BID, enalapril 10mg BID, furosemide 40mg daily. One year later admitted to a local hospital with acute renal failure. All previous medications discontinued. Glargine insulin prescribed twice daily and regular insulin by sliding scale. Although glucose control varied over the years, his renal function markedly improved and remained stable through the period.



[4]

3. High Incidence of Acute Renal Failure

42 Y WF, Hospital Admission , August 2012

- **Admitting Diagnosis**: Vomiting, Low BP and ARF. History of Hypertension
- **Home Medication**: Amitriptyline, Fluoxetine, Clonidine patch and Telmisartan (Micardis ®) 40mg daily and HCTZ 25mg daily.
- **BP** 75/30

42 y WF (Continued)

- Telmisartan discontinued
- Bicarbonate Infusion (900 ml normal Saline Solution + Sodium bicarbonate 100 ml = 1000 ml) started at 60 ml/ hour for 72 hours.
- Her BP increased rapidly requiring Atenolol 50mg P.O. daily and Chlorthalidone 25mg P.O. which brought her BP down to normal level

[6]

Serial Lab shown next

42 y WF (Continued)

Date 2012	BUN/Scr (mg/dL)	eGFR (ml/min)	Na+/ K+ (mmol/L)	C02 (mmol/L)	Hb (g/dL)
Aug 01	24/4.27	12	129/4.6	22	9.4
Aug 02	17/2.46	23	133/5.2	23	10.5
Aug 03	13/1.73	34	136/3.9	30	8.7
Aug 06	11/1.22	52	136/4.7	26	10.9
Aug 7	10/1.13	56	134/4.7	25	11.6

Scr= serum Creatinine eGFR= estimated glomerular filtration rate
Hb= Hemoglobin

- Patient retook Telmisartan by mistake after returning home.
- Developed persistent vomiting and readmitted to hospital
- Sodium Bicarbonate Infusion given

Date 2012	BUN/Scr mg/dL	eGFR ml/min	Na+/K+ mmol/L	Co2 Mmol/L
Aug 11	27/3.90	14	136/3.3	25
Aug 12	26/4.26	12	134/3.5	22
Aug 13	16/2.68	21	135/3.6	31
Aug 14	12/2.24	26	140/4.1	32
Aug 15	10/1.93	30	136/3.7	33
Aug 16	10/1.82	33	141/4.3	30
Aug 17	7/1.67	36	140/4.4	27
Dec 15	11/1.74	34	137/4.5	26
Office visit in 2014				
Feb 25	20/1.32	47	134/3.0	29

3. Causality of ACEI-ARF lead to high incidence of ESRD in diabetes

Acute kidney injury episodes are associated with cumulative risk for CKD in diabetes independent of other risk factors of progression [1].

[1] Thakar CV, etal. Clin J Am Soc Nephrol 2011; 6: 2567-2572

The *power of commercial interest for high Incidence of ESRD*

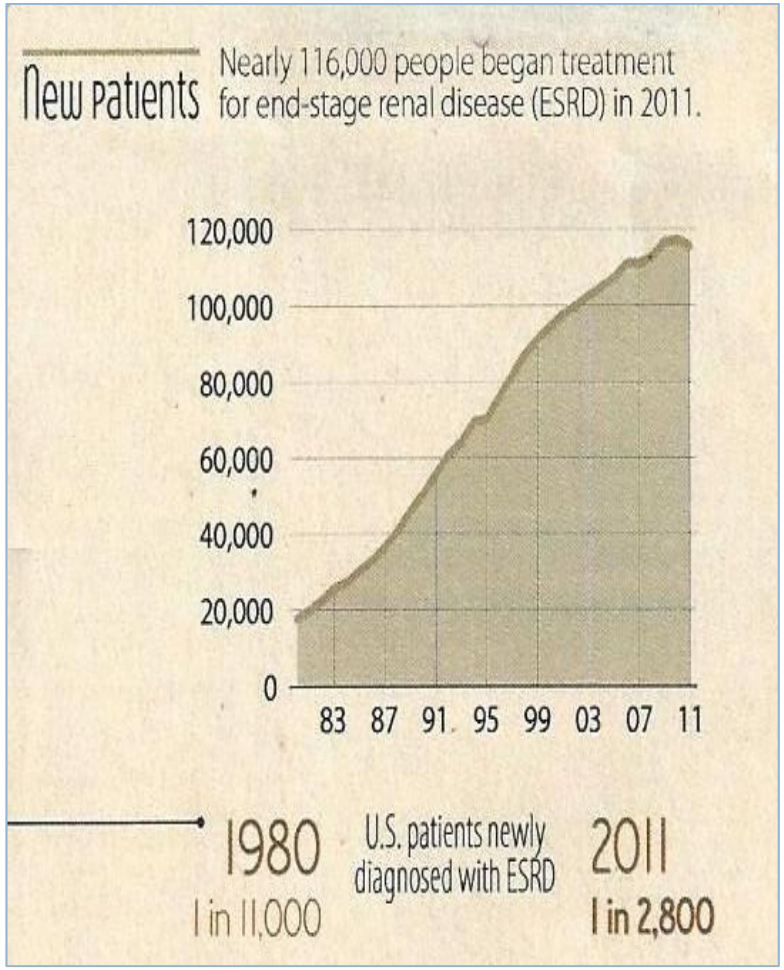
The pendulum has swung from ***glycemic control*** to ***proteinuria control***, even to microalbuminuria control with ACEI and/or ARB. A published report described these drugs as renoprotective in diabetes.*

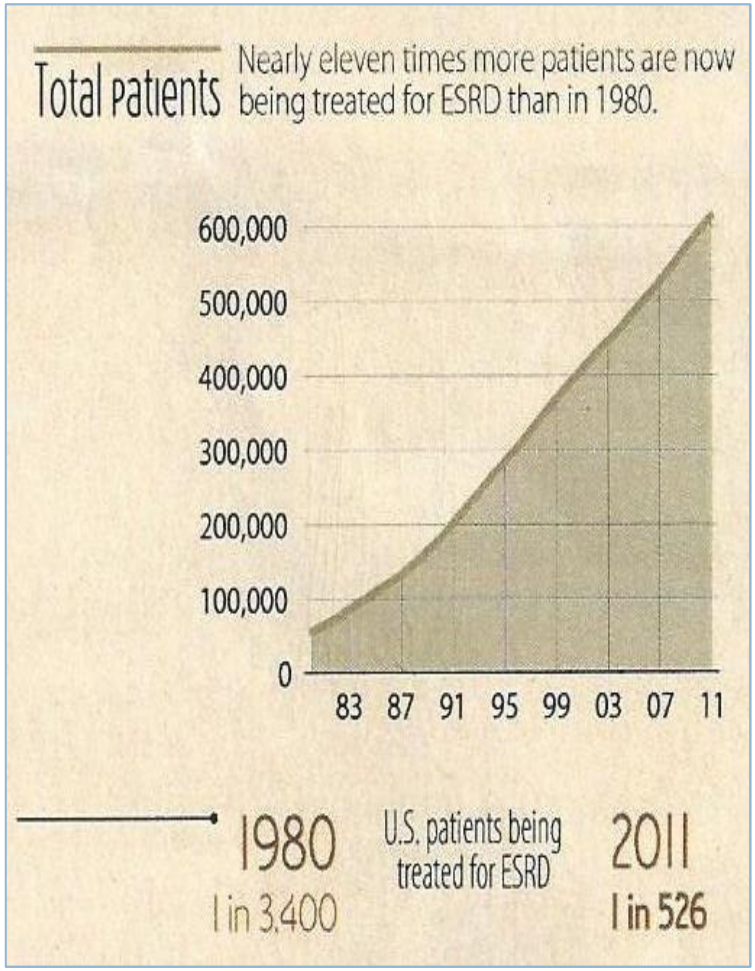
*Lewis EJ. The effect of angiotensin converting enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993; 329: 1456-1462.

Result: High incidence of ESRD.

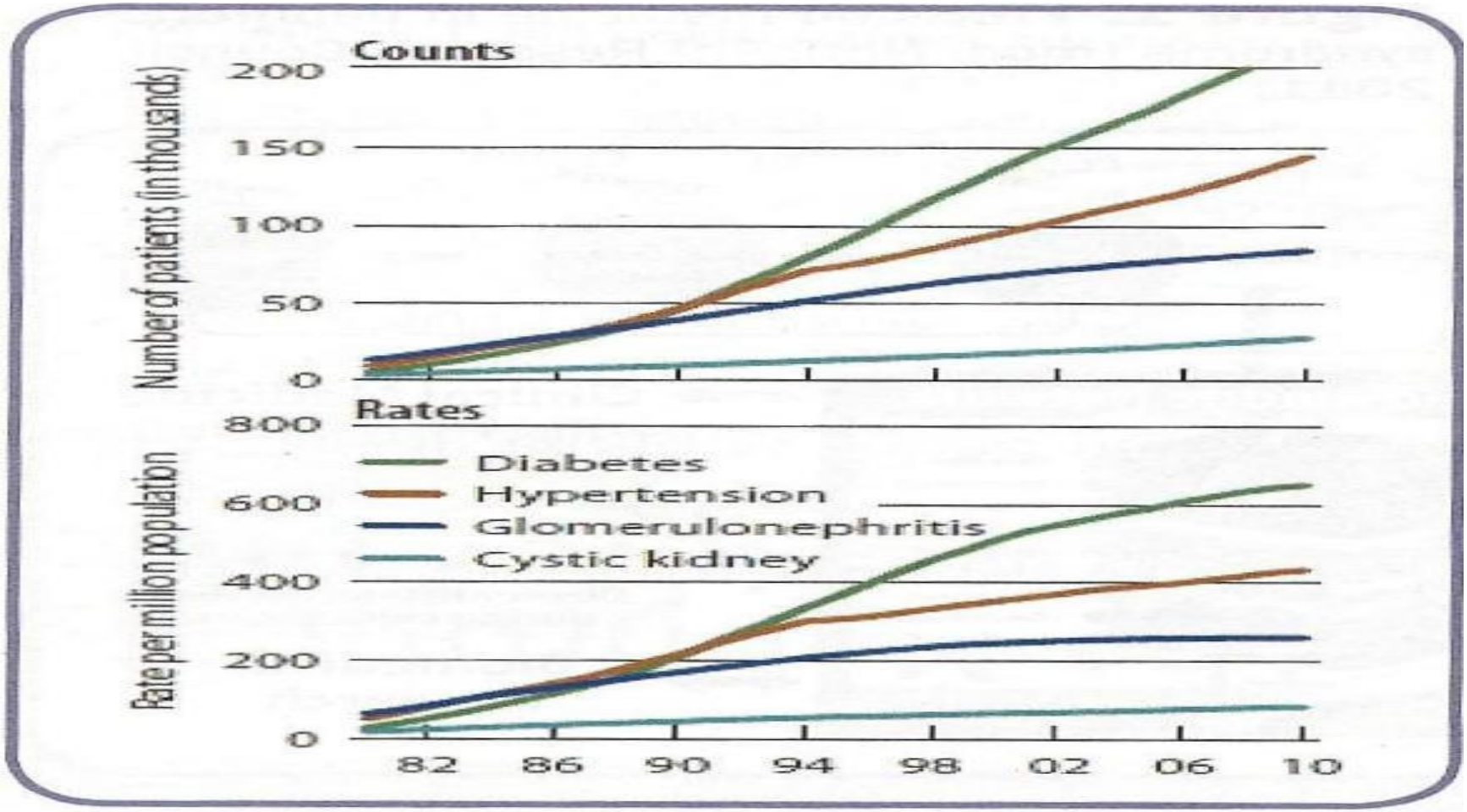
Question:

Why do so many patients including diabetics develop ESRD?





US RENAL DATA SYSTEM
Incidence of ESRD by Primary Diagnosis



[12]

QUESTION: Again Why and How?

New Horizon (Intent)

Intent: Preservation of Renal Function in Diabetes

Steps taken by presenter to accomplish the goal:

1. Understanding pathobiology of high glucose medium (hyperglycemia) on vascular lining cells (endothelial cells).
2. Impact of 2hPPG on renal function.
3. Innovation of dglucose as Predictor of Renal Function
4. Effect of new paradigm of insulin therapy and **complete exclusion of use of ACEI/ARB** in treating diabetes.

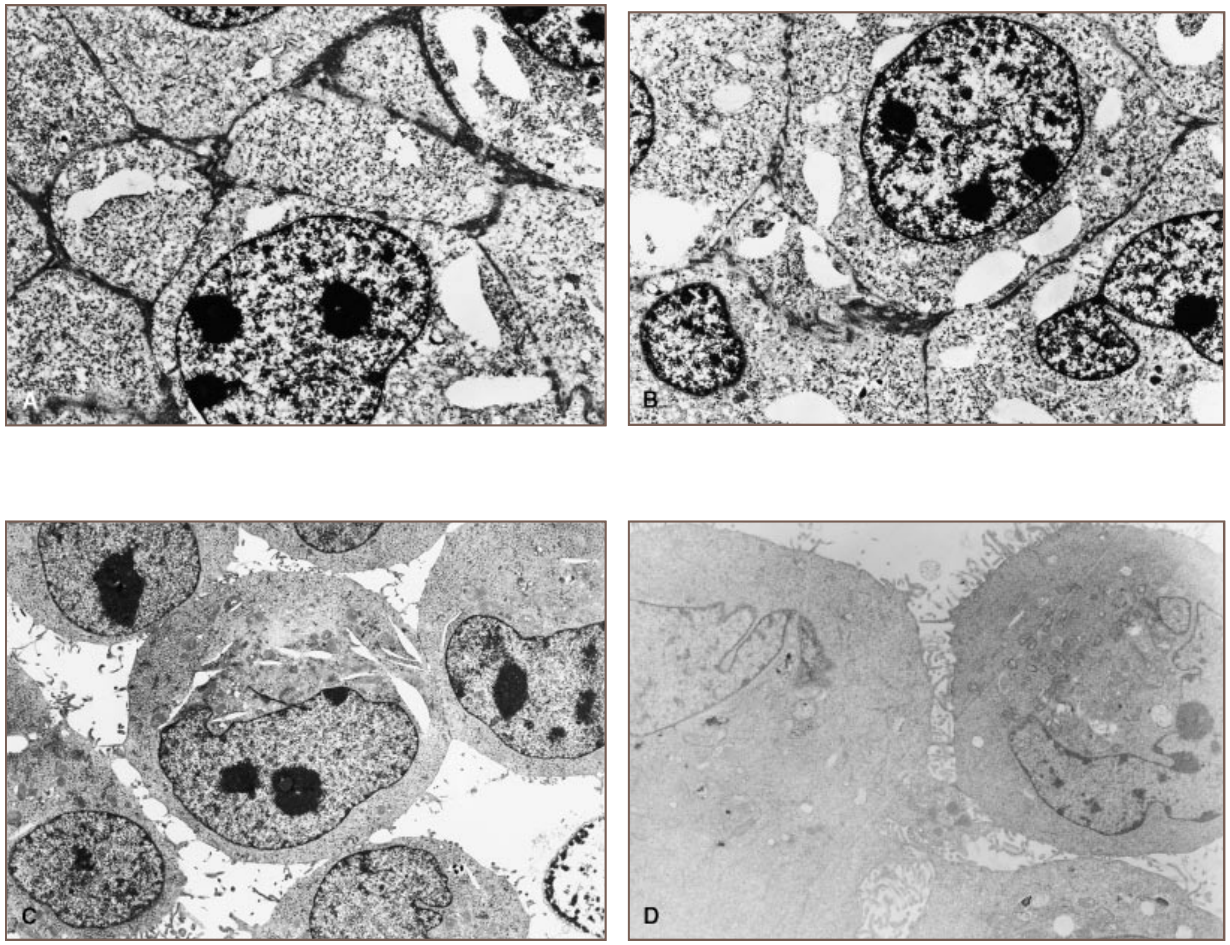
2hPPG= 2-h Postprandial Glucose

Pathobiology of High Glucose

Mandal, et.al. Kidney Int 2000; 57: 2492 – 2501
Mandal, et.al. Histol Histopathol 2006; 21: 941-950

1. Vascular endothelial cells (ECs) of porcine and human origin cultured for growth of cells and treated with normal concentration of glucose (90mg/dL or 5mmol/L) or high concentration of glucose (540mg/dL or 30mmol/L) for 2, 6 or 10 days.
2. Why vascular ECs and not other cell types? Evidence indicates that vascular ECs are most vulnerable to injury by high glucose levels.
   Brownlee M. Diabetes 2005; 54: 1615 - 1625
3. Scanning and transmission electron microscopy done to assess detailed morphological changes.

Transmission electron microscopy study of ECs.



(**A**) ECs treated with FCS (control) show complete adhesion between cells with intact intercellular membrane (36500).
(B) ECs treated with physiological concentration of glucose (5 mmol/L or 90 mg/dL) show no difference from control study (36500).
(C) ECs treated with pathological concentration of glucose (30 mmol/L or 540 mg/dL) show wide separation of the cells (as in Figs. 1B and 2A) with complete loss of intercellular microvilli. Intercellular microvilli have disappeared or fragmented (36500).
(D) Ecs treated with pathological concentration of glucose and insulin (20U/100 mL) show adequate intercellular microvilli and adhesion (36500).
C = crystalline structures suggesting glucose crystals in the middle cell.

[15] adapted from: Mandal, et.al., Kidney Int 2000: 57: 2492-2501

Unified Mechanism for Microvascular complications

Damaged Vascular Ecs

⇩

Shed off

⇩

Occlusion of microvascular apparatus

⇩

Slow ischemia

[16]

Brownlee M: Pathophysiology of diabetic complications: a unifying mechanism in Diabetes 2005; 54: 1615-1625

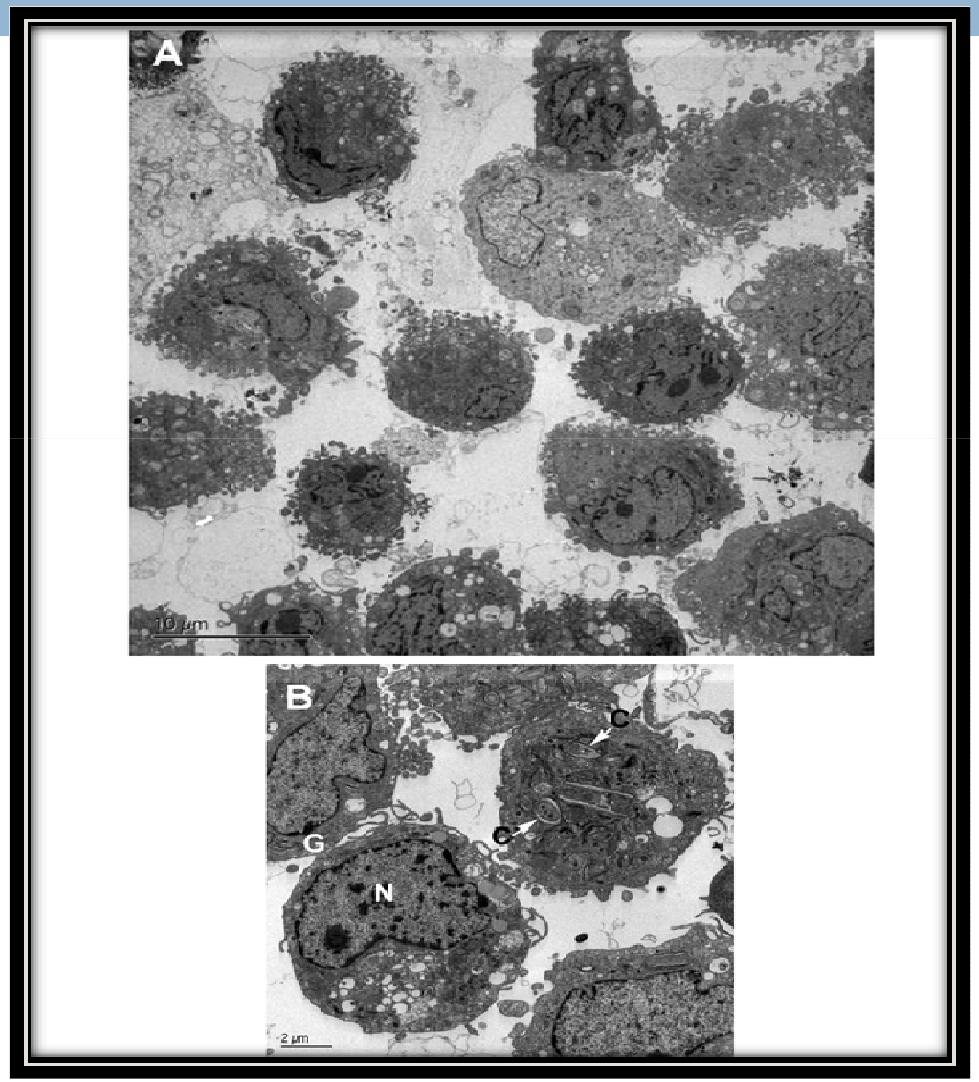
Prevention of Endothelial Cell Damage

Treatment of high glucose with insulin results in mitigation of ECs damage and repair as shown

Endothelial Cell Damage (continued)

A. Glucose and Insulin

B. Glucose + Insulin + Heparin



Impact of 2hPPG

Patients with 2hPPG

≥ 11.1 mmol/L (≥200mg/dL) even when FBG was unequivocally normal, are at the highest risk of developing complications*.

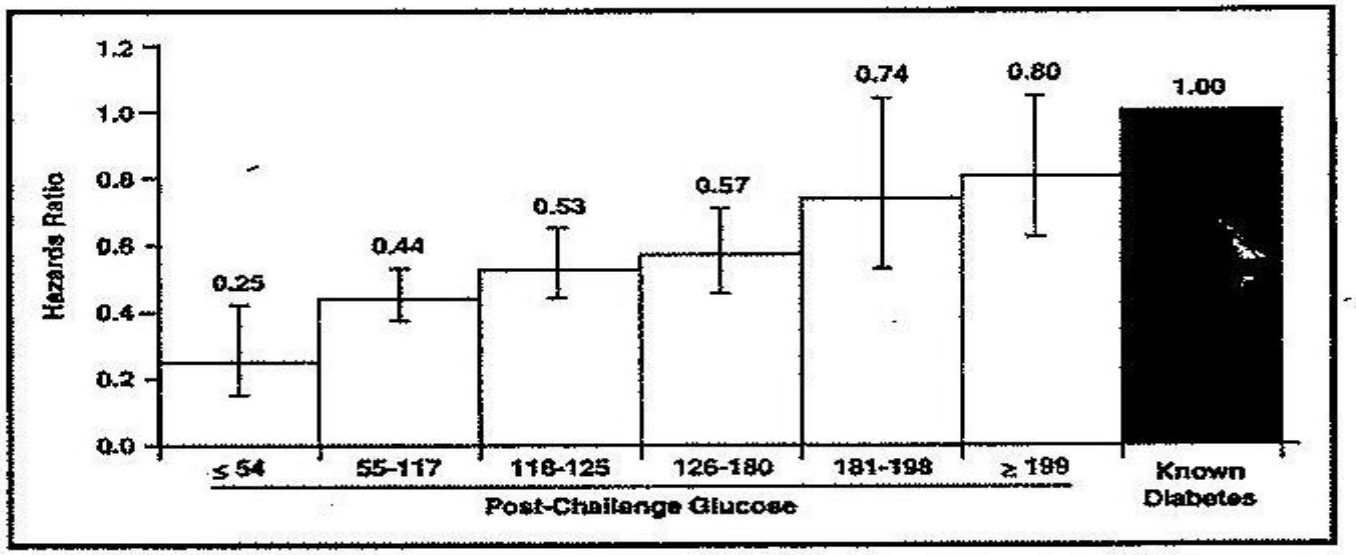
* Harris MI. Undiagnosed NIDDM: Clinical and public health issues. *Diabetes Care* 1993; 16: 642-652

Impact of 2-hPP Hyperglycemia (continued)

2-hPP hyperglycemia is well correlated to cardiovascular disorders in many studies. One such study is illustrated on the next slide.



Impact of 2-hPP Hyperglycemia (continued)



2. The risk for cardiovascular death increases threefold as 2-hour postchallenge glucose levels increase from 54 to 199 mg/dl, although these readings are all in the nondiabetic range. Data were adjusted for age, gender, weight, systolic blood pressure, cholesterol, and smoking during the 11 years of follow-up for the 29,714 patients in the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE)

Decode Study Group. Is the current definition of diabetes relevant to mortality risk from all causes and cardiovascular and non-cardiovascular disease? *Diabetes Care* 2003; 26: 288-696

Paradigm of Therapy

by Mandal Diabetes Research Foundation

In order to obviate the dilemma between FBG and 2hPPG, we innovated the factor of dGlucose (2hPPG – FBG).

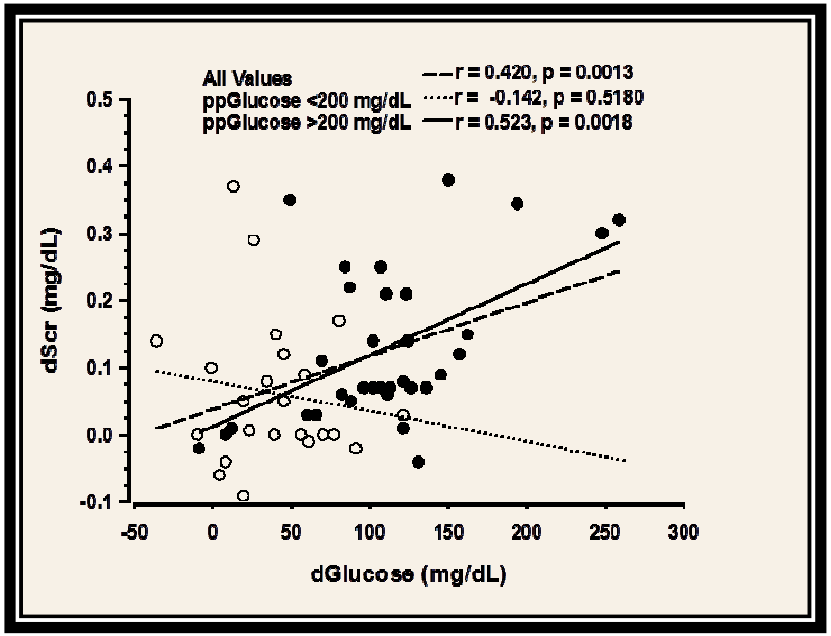
This is shown on the next two slides.



Paradigm of Therapy by
Mandal Diabetes Research Foundation

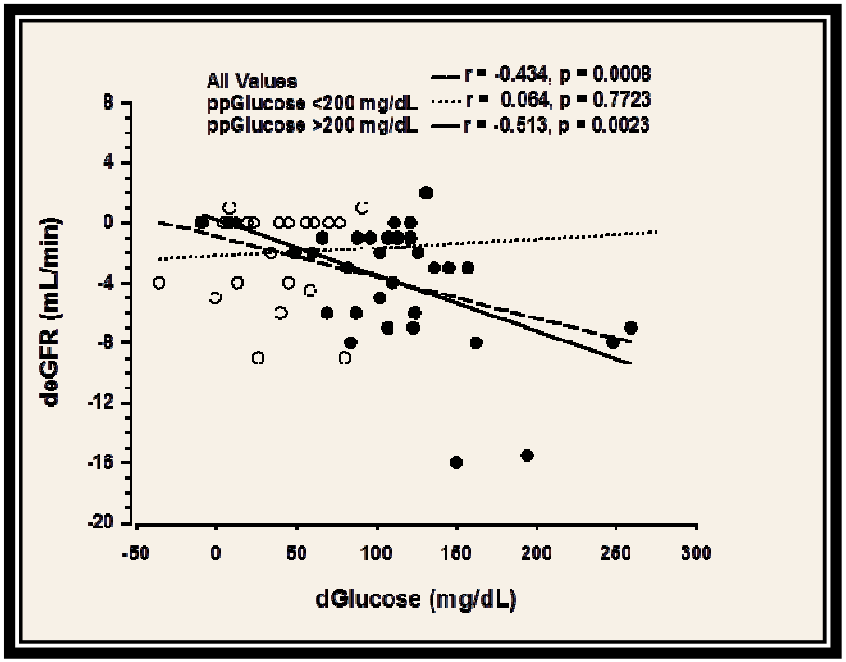
- A novel approach with introduction of *dGlucose* (2hPPG – FBG) and related dglucose results with the same calculated differences for serum creatinine (dscr) and estimated glomerular filtration rate (deGFR) in a study of 56 insulin treated diabetic subjects.
  - Mean age 68.7 $\pm$ 13.5 (years)

Results shown in next slide.



Correlation between dScr and dglucose and correlation coefficients and *p* values are shown for all 56 patients (dashed line, all data points), for patients whose 2hPP glucose is greater than 200 mg/dL (solid line, black circles, *n* = 33) and for patients whose 2hPP glucose is less than 200 mg/dL (dotted line, open circles, *n* = 23)

Correlation between deGFR and dglucose and correlation coefficients and p values are shown for all 56 patients (dashed line, all data points), for patients whose 2hPP glucose is greater than 200 mg/dL (solid line, black circles, *n* = 33) and for patients whose 2hPP glucose is less than 200 mg/dL (dotted line, open circles, *n* = 23).



Figures Adapted from Mandal AK and colleagues. *Diab Res Clin Pract* 2011; 91: 190-194

Control of dglucose (2hPP-F) is Fundamental to Renal Preservation in Diabetes (in Preparation)

1. We previously reported that dglucose is predictive of renal function changes in diabetes
2. This is an expanded study
3. 85 diabetic patients M: F 34:51 60.8 ± 13.8 years
4. Mean Duration of Treatment 26.3 ± 24. 6 months
5. Diabetes Treatment: Combination of Glargine or detemir (12 h apart) and regular insulin before meals and bedtime.
6. BP control: Any antihypertensive drug with **exclusion of ACEI/ ARB drugs.**

Results (ISD) Explain

Variable	First Visit	N	Last Visit	P Value
FBG (mg/dl)	175.2 ± 83.6	59	166.2 ± 87.9	NS
2hPP (mg/dl)	244.0 ± 98.2	57	217.2 ± 94.8	NS
FScr (mg/dl)	1.11 ± 0.44	60	1.11 ± 0.45	NS
2hPP SCR (mg/dl)	1.22 ± 0.53	50	1.27 ± 0.60	NS
FeGFR (ml/min)	68.2 ± 26.3	60	65.8 ± 26.3	NS
2hPP eGFR (ml/min)	61 ± 24.3	50	58.3 ± 23	NS
Dglucose (mg/dl)	**63.5 ± 68.1**	**41**	**36.6 ± 65.6**	**0.0449**
Siting SBP (mmHg)	**133.1 ± 17.1**	**74**	**128.4 ± 13.9**	**0.0319**
Sitting MBP (mmHg)	**98.9 ± 11.3**	**74**	**95.41**	**0.0151**
HbA1c (%)	8.2 ± 2.0	29	8.2 ± 1.8	NS

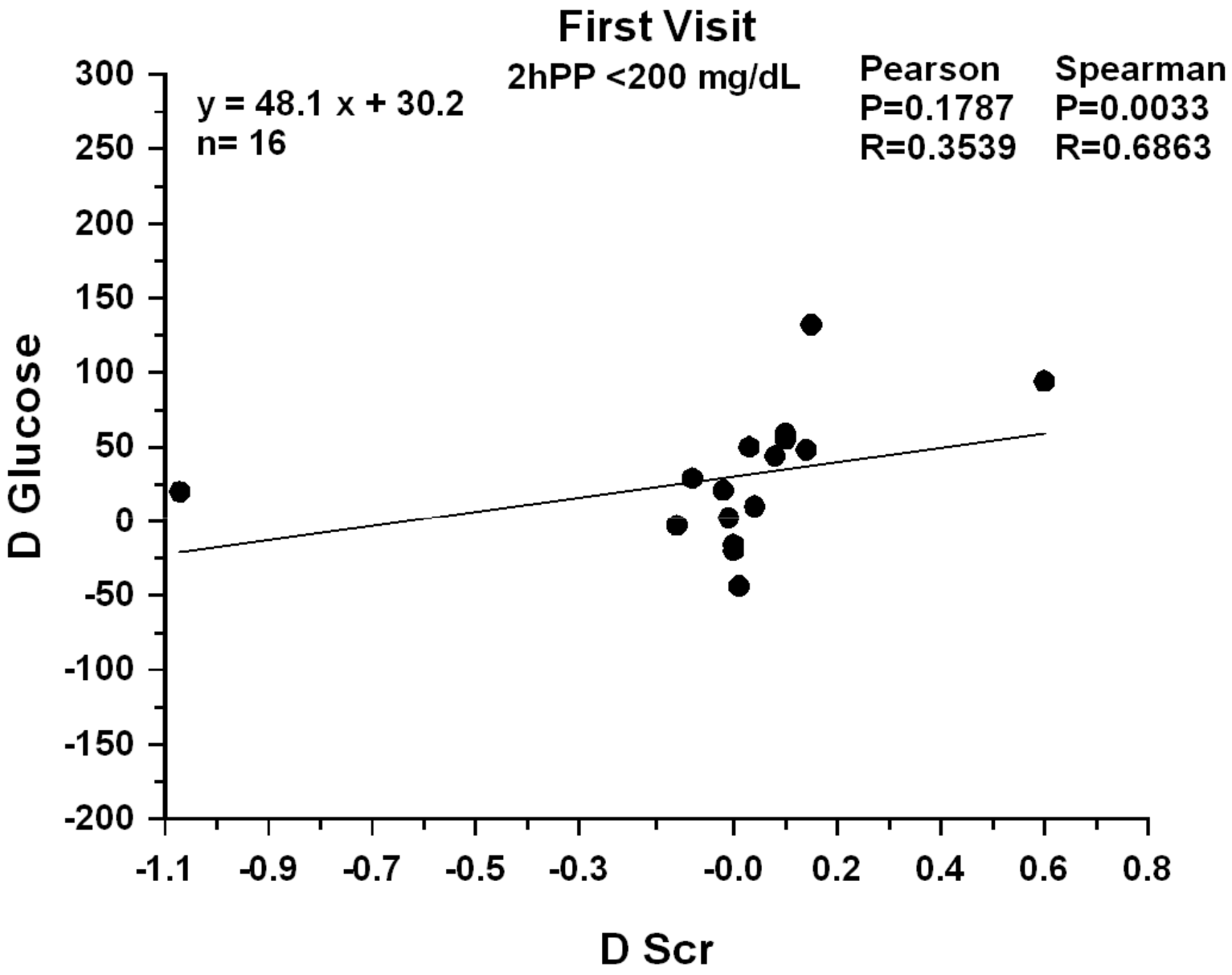
[26]

SBP=Sitting systolic blood pressure
MBP=Mean arterial blood pressure

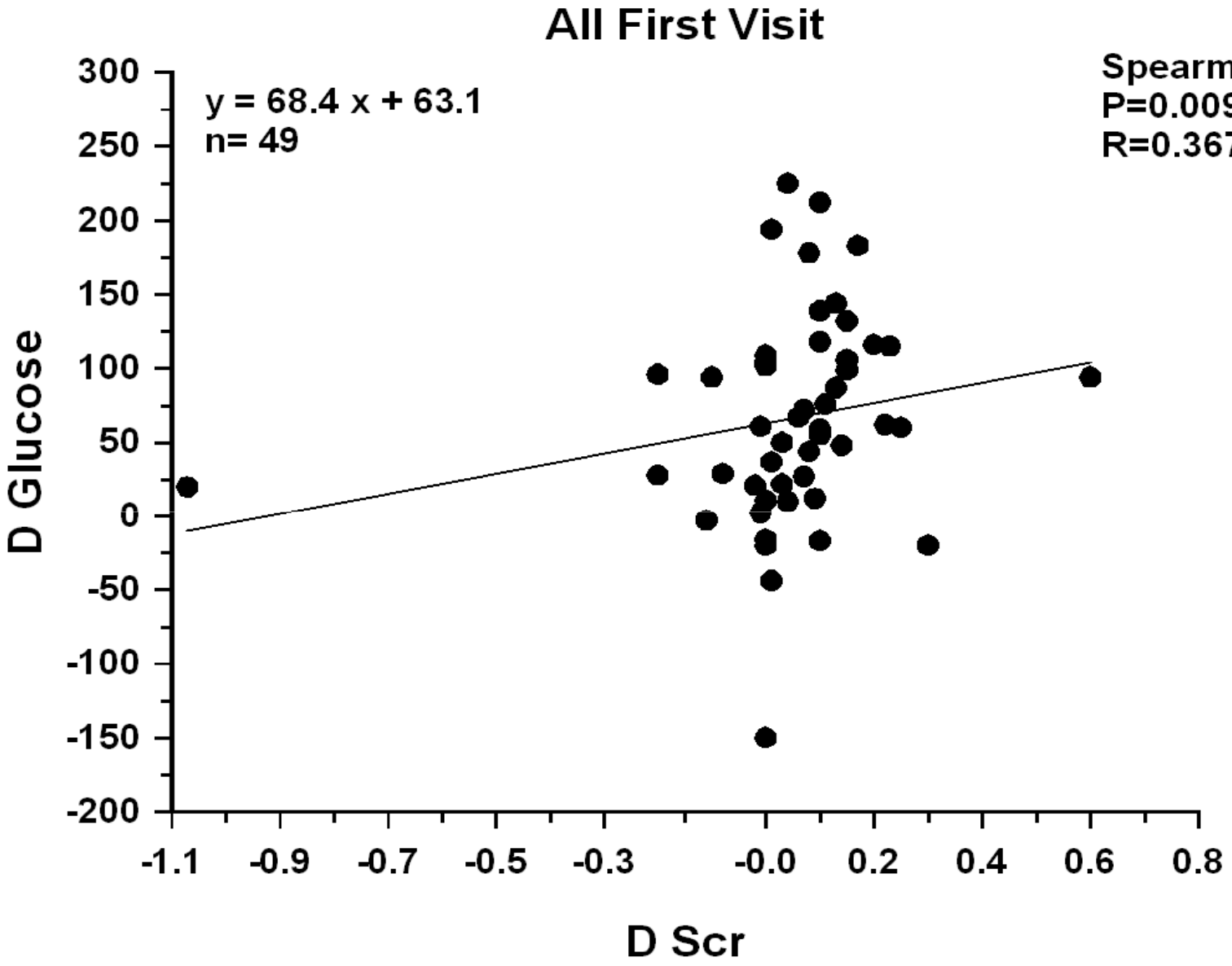
Correlation Between dglucose and drenal function Parameters

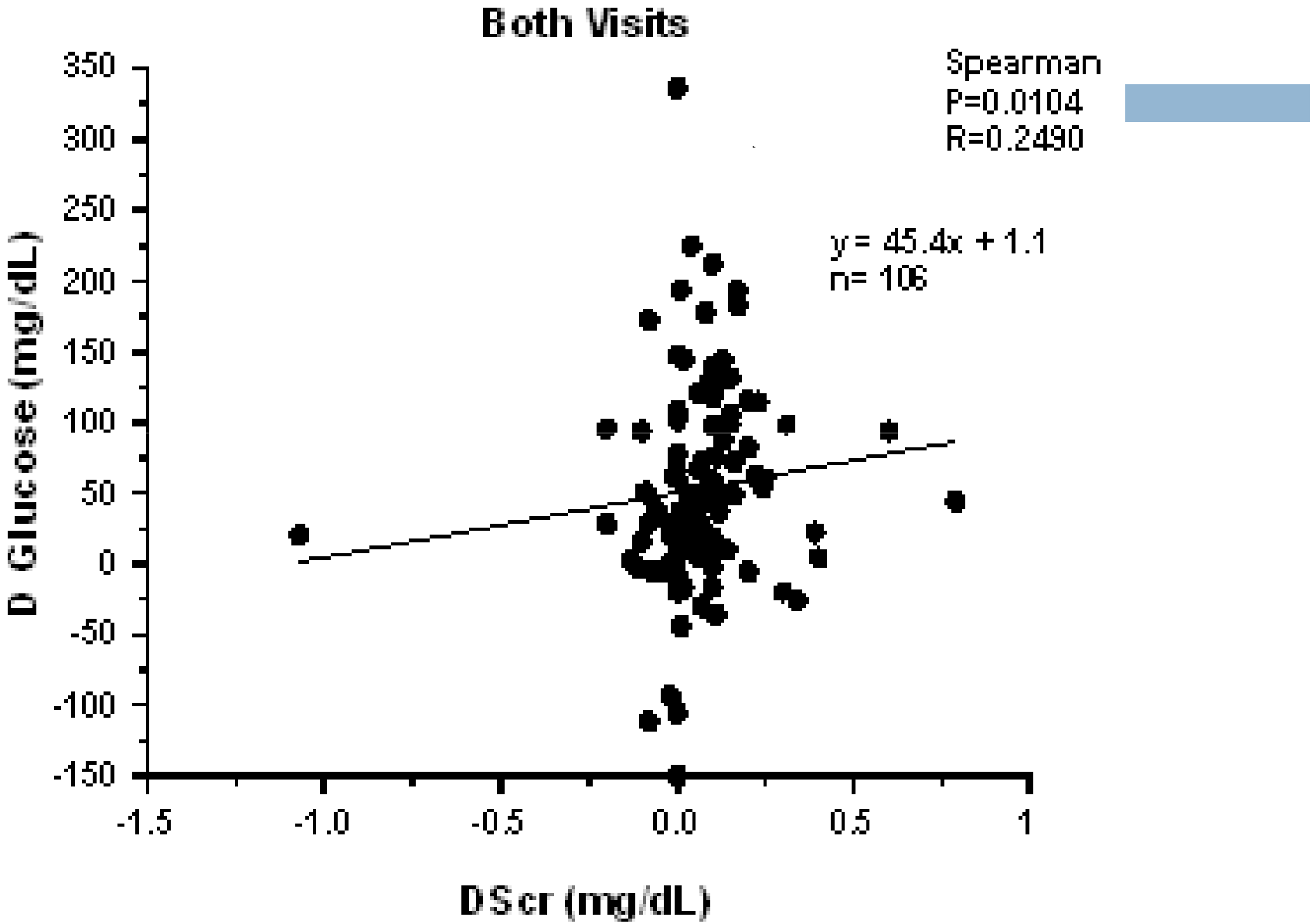
Shown NEXT



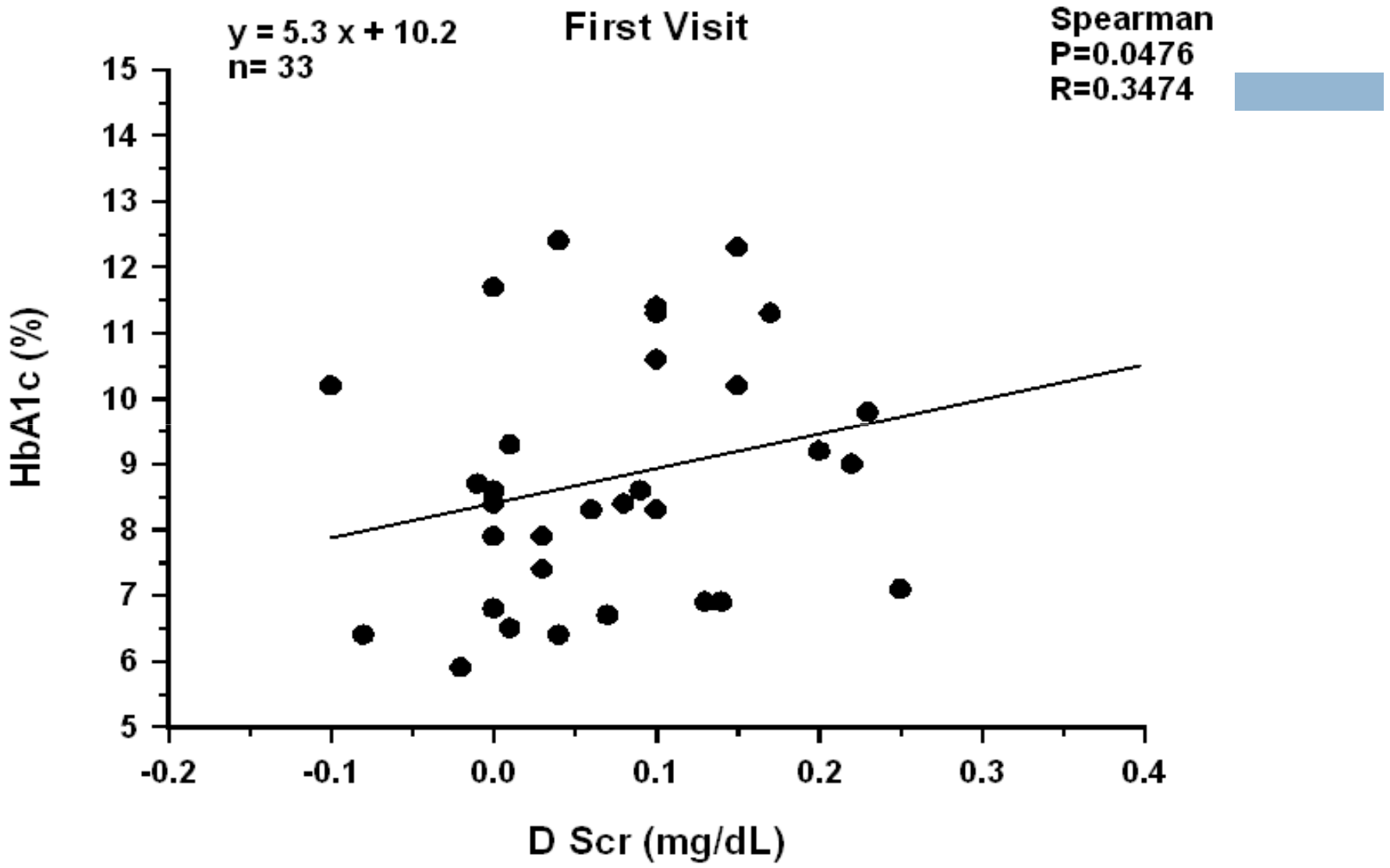

First Visit
2hPP <200 mg/dL
y = 48.1 x + 30.2
n= 16
Pearson
P=0.1787
R=0.3539
Spearman
P=0.0033
R=0.6863
D Glucose
300
250
200
150
100
50
0
-50
-100
-150
-200
-1.1
-0.9
-0.7
-0.5
-0.3
-0.0
0.2
0.4
0.6
0.8
D Scr

[28]

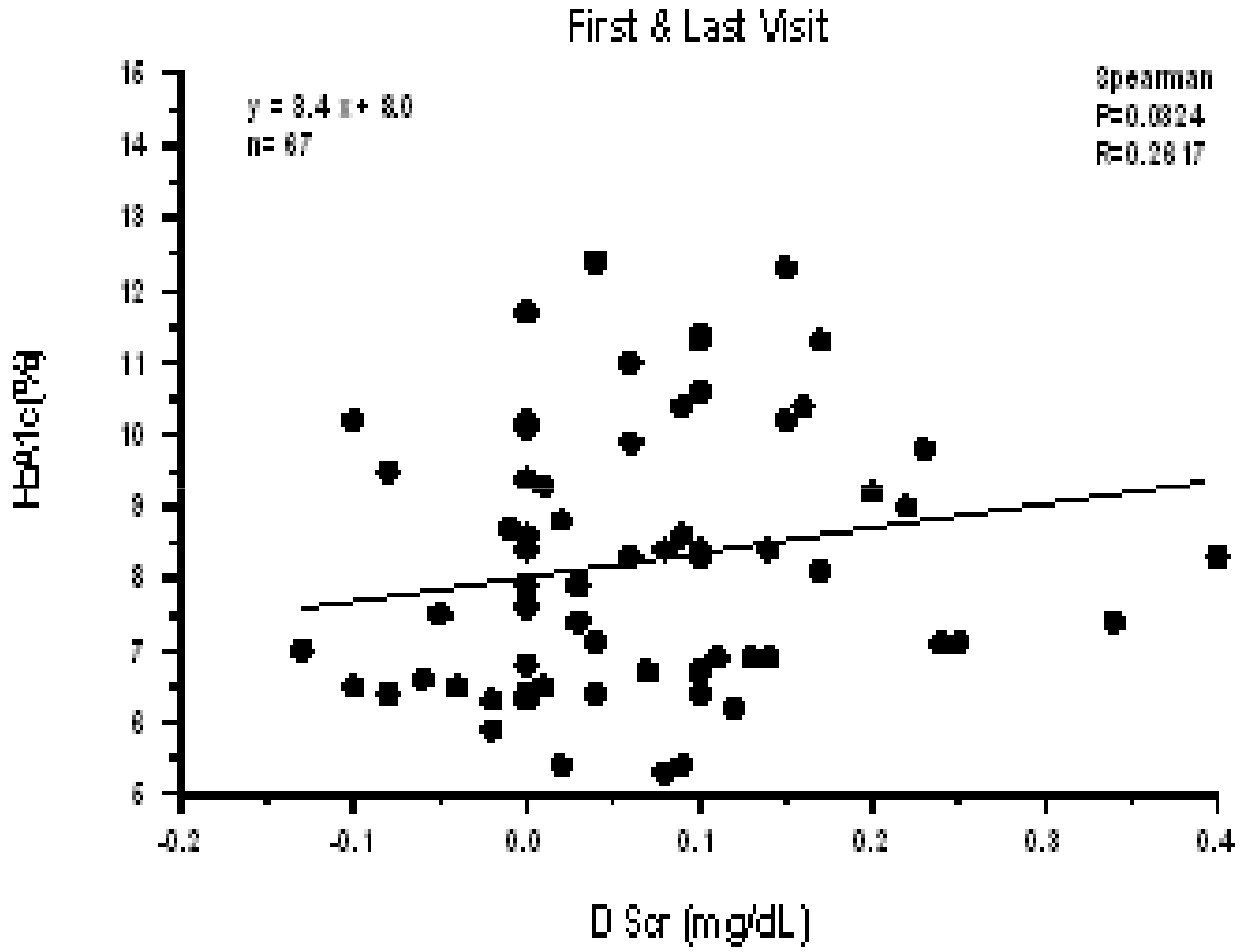

All First Visit
y = 68.4 x + 63.1
n= 49
Spearman
P=0.0094
R=0.3676
D Glucose
D Scr
300
250
200
150
100
50
0
-50
-100
-150
-200
-1.1
-0.9
-0.7
-0.5
-0.3
-0.0
0.2
0.4
0.6
0.8


Both Visits
Spearman
P=0.0104
R=0.2490
y = 45.4x + 1.1
n= 106
D Glucose (mg/dL)
DScr (mg/dL)
350
300
250
200
150
100
50
0
-50
-100
-150
-1.5
-1.0
-0.5
0.0
0.5
1

[30]

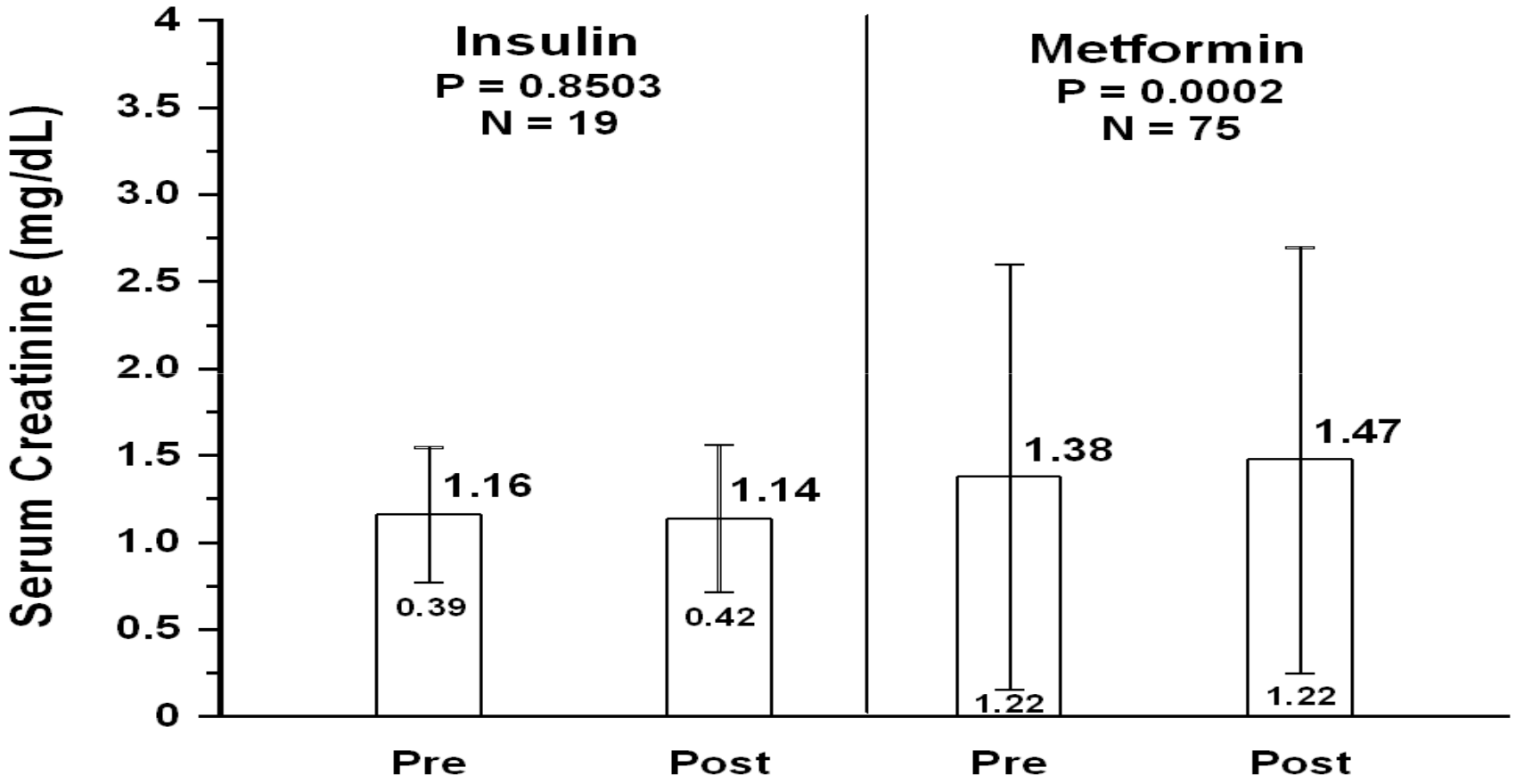

y = 5.3 x + 10.2
n= 33
First Visit
Spearman
P=0.0476
R=0.3474
HbA1c (%)
D Scr (mg/dL)
15
14
13
12
11
10
9
8
7
6
5
-0.2
-0.1
0.0
0.1
0.2
0.3
0.4

[31]


First & Last Visit
y = 8.4 x + 8.0
n= 67
Spearman
P=0.0824
R=0.2617
HbA1c(%)
D Scr (mg/dL)
16
14
12
11
10
9
8
7
6
-0.2
-0.1
0.0
0.1
0.2
0.3
0.4

[32]

Serum Creatinine comparing Pre and Post Treatment in Insulin or Metformin Treated Patients



Serum creatinine was significantly increased in metformin but not insulin treated patients. Mean ± SD.

[33]

To be presented in American Society of Nephrology, November 15, 2014, Philadelphia

PEARL OF WISDOM

1. **Renal function preservation in diabetes is attainable with insulin therapy and vigilant care***

**Mandal AK. Frequent Office Visits of patients with Chronic Kidney Disease is a prelude to prevention of dialysis. World Jour Nephrol 2014; 6: 1-5.*

2. **Application of d (2hPP-F) glucose is essential to determine relationship between glycemic control and renal function changes.**

3. **Thus it is essential to order Fasting and 2hPP basic metabolic panel in all diabetes patients**

4. **Our studies reinforce the importance of exclusion of ACEI/ARB in prevention of ESRD in diabetes.***

**To be presented in American Society of Nephrology November 15, 2014, Philadelphia*

Reminiscent of Discovery of Diabetes and Insulin

1. **Diabetes mellitus is due to a deficiency of the internal secretion of the pancreas. The main principle of treatment is to correct this deficiency.**
2. **If it is found that the patient is unable to keep sugar-free on a diet that is compatible with an active, useful life, sufficient insulin is administered to meet this requirement.**
3. **In severe cases, insulin to be administered subcutaneously three times daily, from one-half to three-quarters of an hour before meals. This was done so that the curve of hypoglycemia produced by insulin was superimposed on the curve of hyperglycemia produced by the meal.**
4. **In rare cases, a small fourth dose of insulin was given at bedtime to control nocturnal glycosuria.**
5. **The less severe cases could be satisfactorily treated on a morning and evening dose, or a single dose before breakfast.**

Banting: Nobel Prize Speech delivered in Stockholm. September 25, 1925

The practice of medicine is an art of observation and not all science.



Thank You