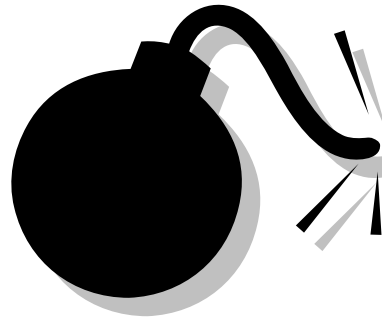
Diyabetik Nefropati Tedavisinde Gelecek 10 Yıl

Dr. Bülent Tokgöz
Erciyes Üniversitesi Tıp Fakültesi
Nefroloji BD

Diyabet ve SDBY

- DM görülme sıklığı % 6-7!
- Nefropati riski % 20-40!
- Böbrek hastalığını durdurma çabaları yeterince başarılı değil!
- Proteinürik hastalar büyük oranda SDBY aşamasına ilerliyor!



National Diabetes Fact Sheet 2005 USA

Diyabetik Nefropati Tedavisi

GÜNCEL TEDAVİLER

Böbrek Hasarını Önleme Çabaları

Kanıtlanmış Tedaviler

Strateji	Kanıt	Yorum
Sıkı kan basıncı kontrolü	MDRD, ABCD, AASK, AIPRD	Hedef kan basıncı: 110-130/75-80
ACE i	Lewis, APRI, REIN, AASK	Hedef proteinüri < 500mg/gün
ARB	RENAAL, IDNT	ACEi intolereansı durumunda ilk seçenek
ACEi + ARB	CALM, COOPERATE	Daha iyi antihipertansif ve antiproteinürik etki
Diyette protein kısıtlaması	MDRD, Kasiske	
Kan şekeri kontrolü	DCCT (Tip 1 DM) UKPDS (Tip2 DM)	

Retardation of Kidney Failure – Applying Principles to Practice
DCH Harris, GK Rangan
Ann Acad Med Singapore 2005;34:16-23

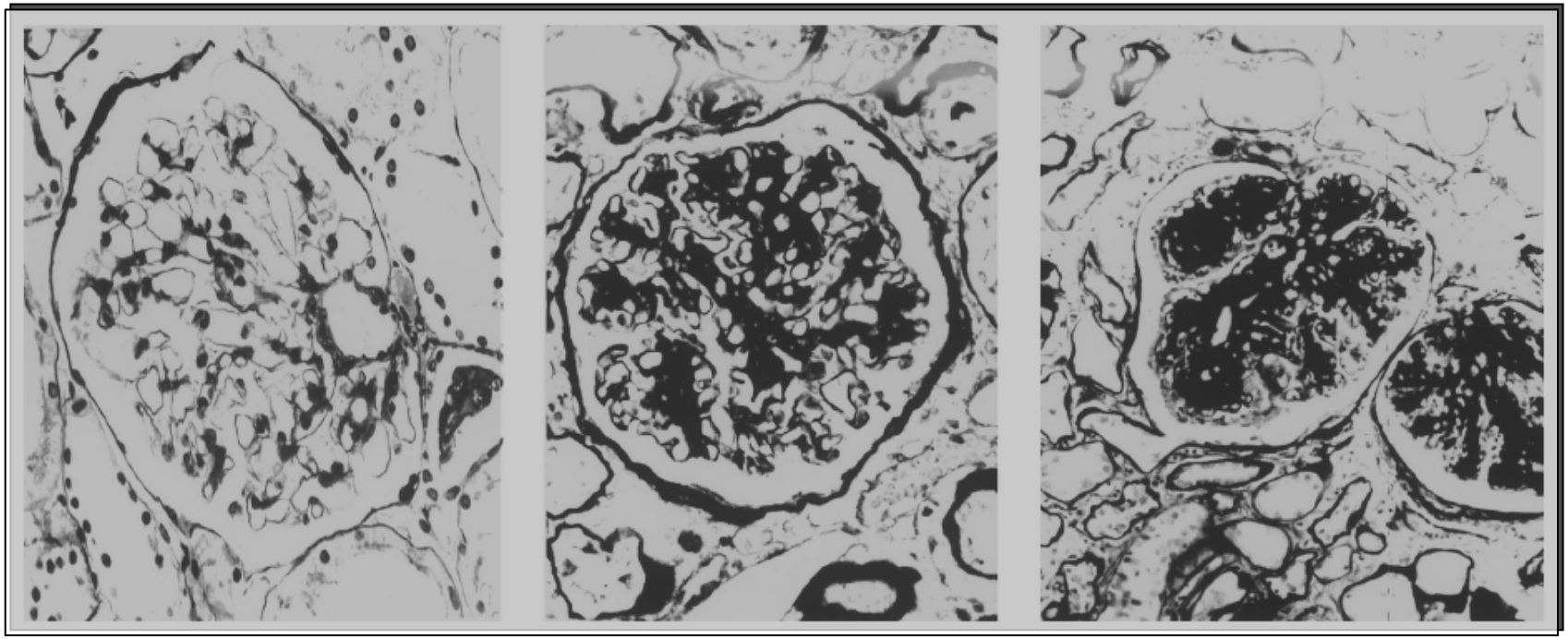
Böbrek Hasarını Önleme Çabaları

Faydalı Olabilecek Tedaviler

Strateji	Kanıt	Yorum
DHKKB kullanmaktan kaçınmak	ABCD, AASK, IDNT	DHKKB proteinüriyi hafifletmiyor
Tuz kısıtlaması		ACEi ve ARB antihipertansif /antiproteinürik etkilerini artırır
Aldosteron antagonisti	Sato	Özellikle tip 2 DM hastalarında etkili
Lipid kontrolü	Fried	Özellikle HMG CoA inhibitörleri
Sigaranın bırakılması	Orth	

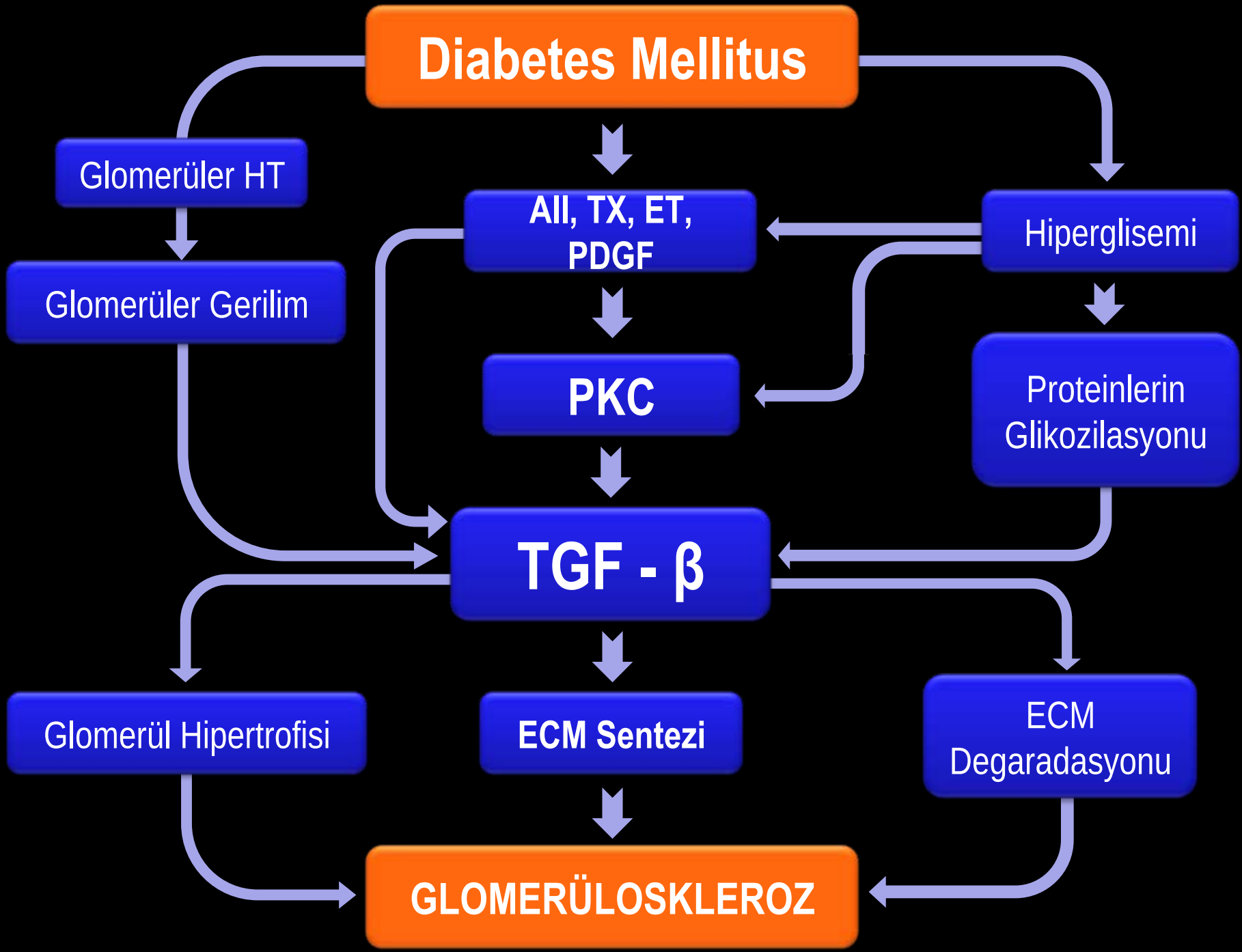
Retardation of Kidney Failure – Applying Principles to Practice
DCH Harris, GK Rangan
Ann Acad Med Singapore 2005;34:16-23

Diyabetik Nefropatinin Doğal Seyri



Normal | Diyabetik Nefropati | İleri Diyabetik Nefropati

- Mezangiyal matriks artışı
- Tübülointerstisyel fibrozis
- Arterioler hyalinozis
- Glomerülosklerozis


Diabetes Mellitus
Glomerüler HT
Glomerüler Gerilim
AII, TX, ET, PDGF
Hiperglisemi
PKC
Proteinlerin Glikozilasyonu
TGF - β
Glomerül Hipertrofisi
ECM Sentezi
ECM Degaradasyonu
GLOMERÜLOSKLEROZ

Diyabetik Nefropati Tedavisi

GELECEK TEDAVİLER

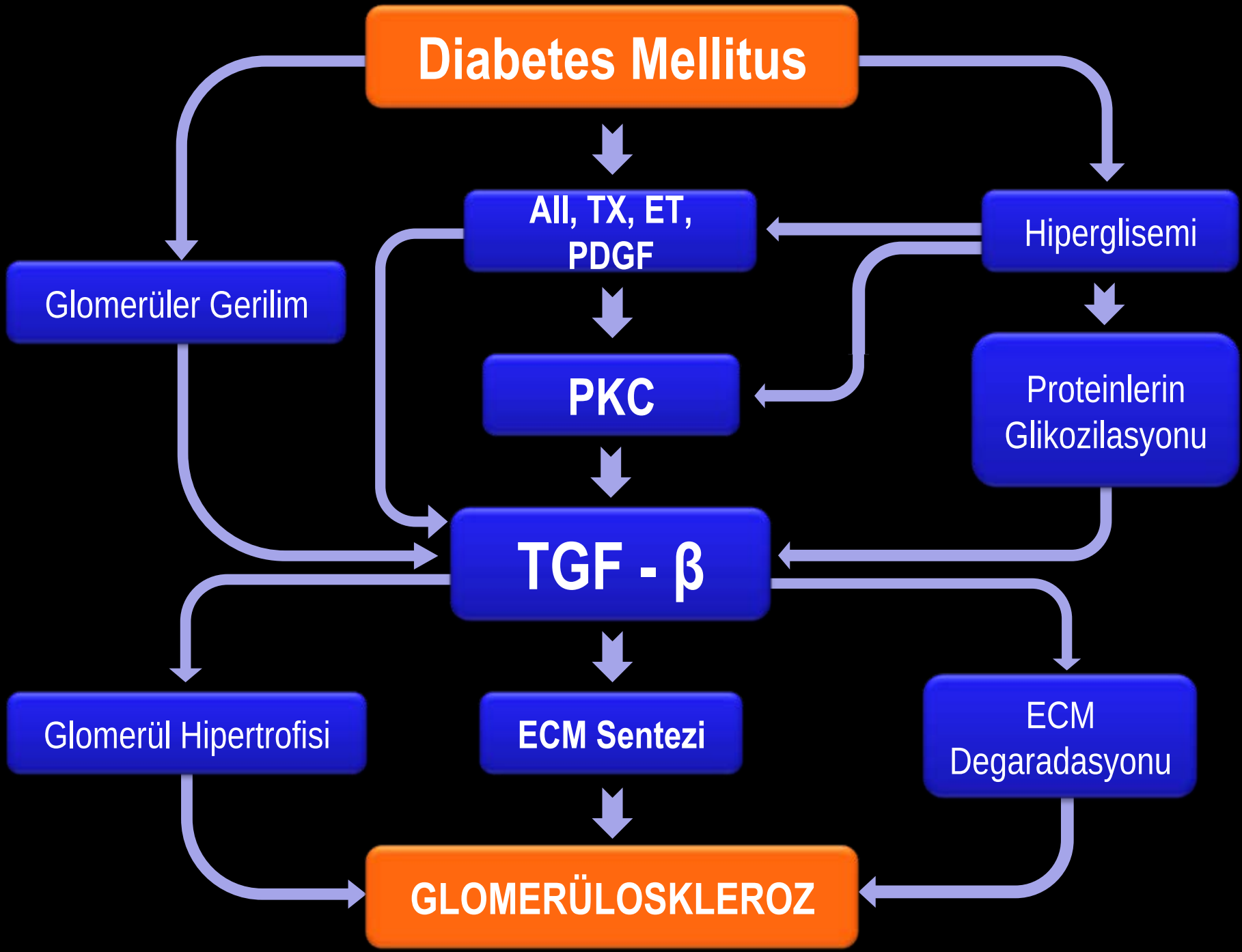
Diyabetik Nefropati

Gelecek Tedaviler

TGF- β inhibisyonu	Pirfenidone
Protein kinaz C inhibisyonu	Ruboxistaurin
Bazal membran restorasyonu	Sulodexide
PPAR Gamma stimülasyonu	Thiazolidinedionlar
Mineralokortikoid inhibisyonu	Sprinolakton
Renin İnhibisyonu	Aliskiren
…	Vitamin D

Diyabetik Nefropati Tedavisi

TGF-β İnhibisyonu


Diabetes Mellitus
AII, TX, ET, PDGF
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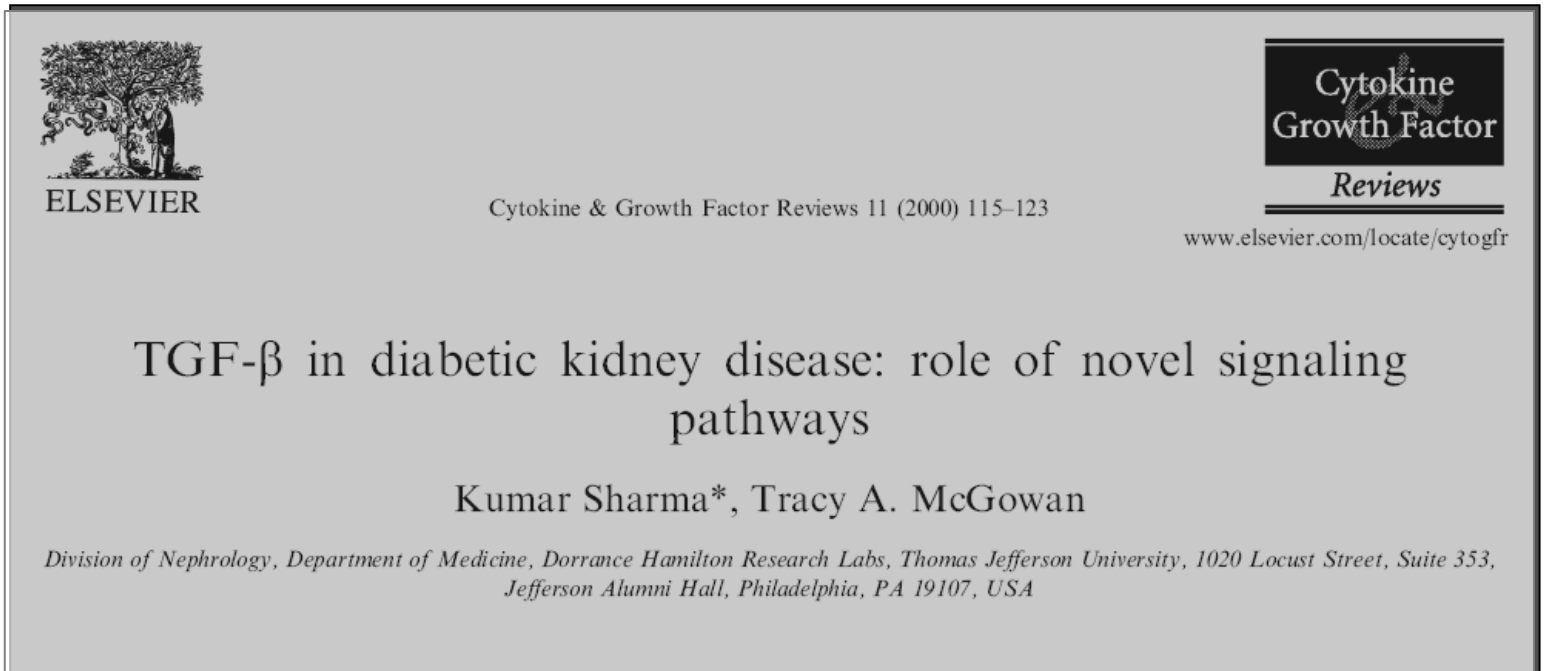
Proteinlerin Glikozilasyonu
TGF - β
Glomerül Hipertrofisi
ECM Sentezi
ECM Degaradasyonu
GLOMERÜLOSKLEROZ

Diyabetik Nefropati

Patogenezde TGF-β

- Erken evrelerde ⇨ glomerül hipertrofisi
- Kronik fazda ⇨ mezangiyal matriks birikimi



ELSEVIER

Cytokine & Growth Factor Reviews 11 (2000) 115–123

Cytokine Growth Factor Reviews

www.elsevier.com/locate/cytogfr

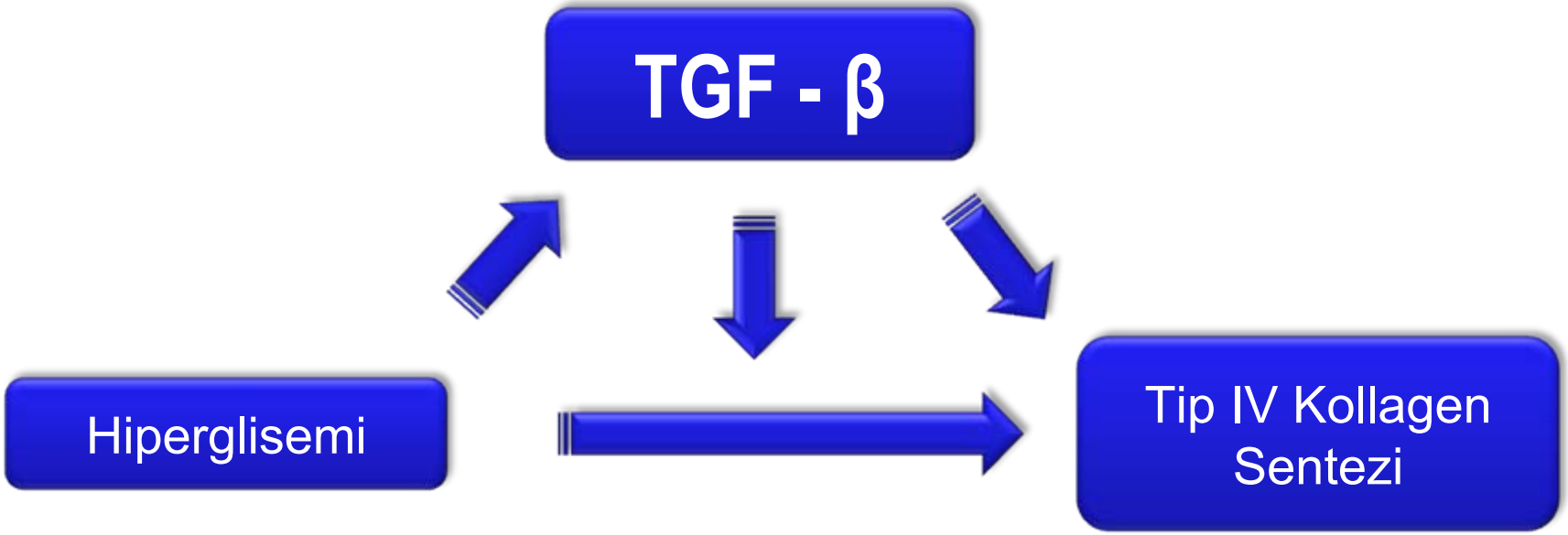
TGF-β in diabetic kidney disease: role of novel signaling pathways

Kumar Sharma*, Tracy A. McGowan

Division of Nephrology, Department of Medicine, Dorrance Hamilton Research Labs, Thomas Jefferson University, 1020 Locust Street, Suite 353, Jefferson Alumni Hall, Philadelphia, PA 19107, USA

Diyabetik Nefropati

Mezangiyal matriks artışının sebebi nedir?



Stimulation of Collagen Gene Expression and Protein Synthesis in Murine Mesangial Cells by High Glucose Is Mediated by Autocrine Activation of Transforming Growth Factor-β

Fuad N. Ziyadeh, Kumar Sharma, Mark Ericksen, and Gunter Wolf*

*Penn Center for Molecular Studies of Kidney Diseases, Renal-Electrolyte and Hypertension Division, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104-6144; and *Department of Medicine, Division of Nephrology, University of Hamburg, Hamburg D-20246, Germany*

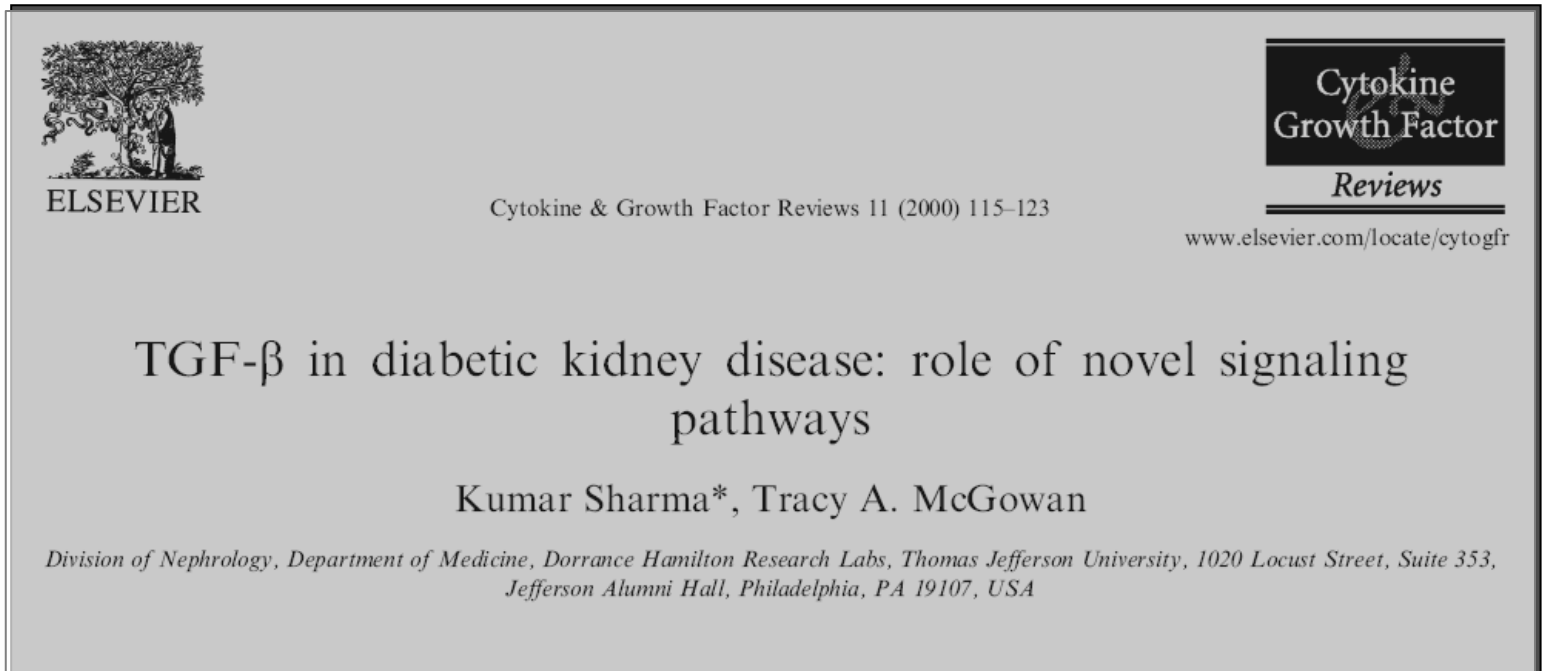
TGF-β Salınımını Uyaran Faktörler

Erken evreler:

- Hiperglisemi
- Protein kinaz C

İleri evreler:

- Glikozile proteinler
- TGF-β oto-indüksiyonu



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TGF-β in diabetic kidney disease: role of novel signaling pathways

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Diyabetik Nefropati
Patogenezde TGF-β

Spontan diyabetik ratlarda:

- Kısa süreli hiperglisemi (3-7 gün) TGF-β ekspresyonunu artırmaktadır!

Am J Physiol Renal Physiol 267: F1094-F1001, 1994;
0363-6127/94 $5.00

AJP - Renal Physiology, Vol 267, Issue 6 1094-F1001, Copyright © 1994 by American Physiological Society

ARTICLES

Renal hypertrophy is associated with upregulation of TGF-beta 1 gene expression in diabetic BB rat and NOD mouse

K. Sharma and F. N. Ziyadeh
Penn Center for Molecular Studies of Kidney Diseases, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia 19104-6144.

Diyabetik Nefropati
Klinik çalışmalarda TGF-β

- Diyabetik hastaların böbreklerinde TGF-β miktarı yüksek…
- Glomerüler TGF-β ekspresyonu glisemik kontrol derecesiyle yakın ilişkili…

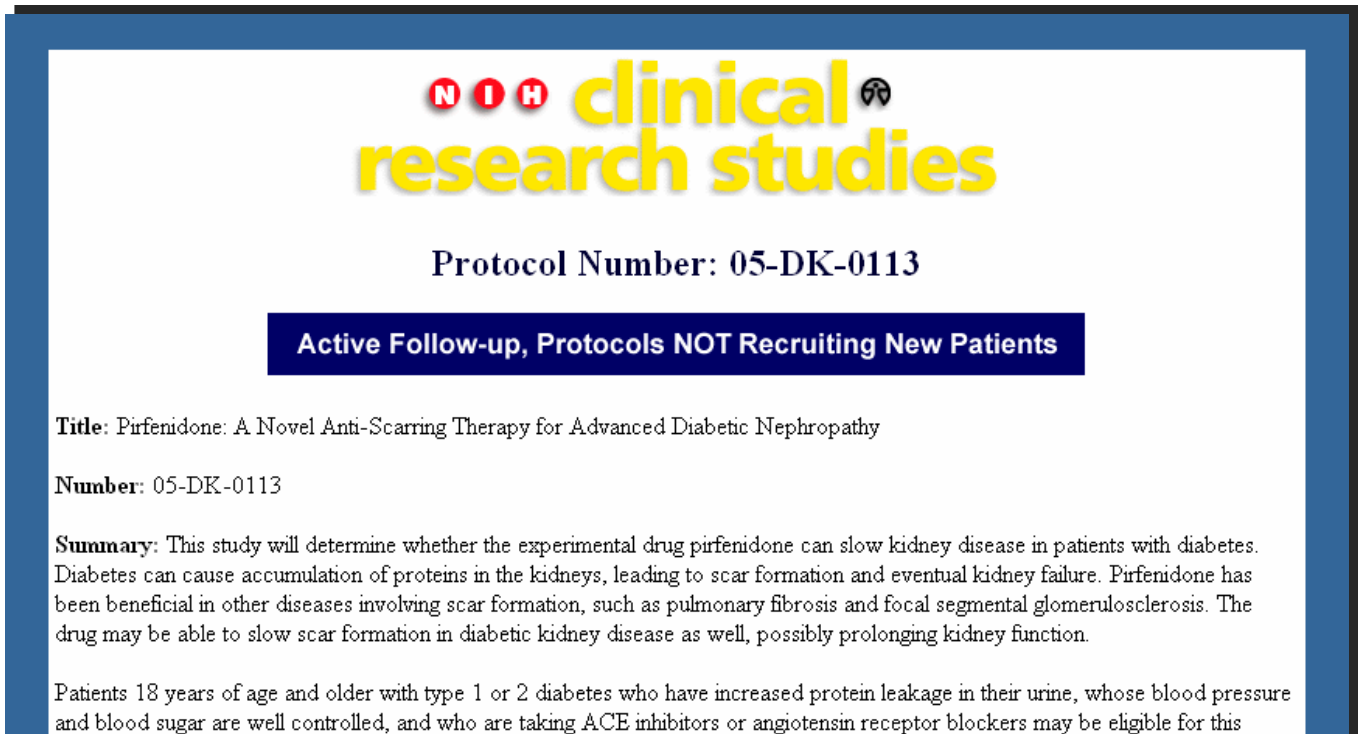
Kidney International, Vol. 49 (1996), pp. 1120–1126

Quantification of glomerular TGF-β1 mRNA in patients with diabetes mellitus

MASAYUKI IWANO, ATSUSHI KUBO, TOSHIHIKO NISHINO, HIROAKI SATO, HISAYUKI NISHIOKA, YASUHIRO AKAI, HIDEYUKI KURIOKA, YOSHIHIRO FUJII, MASAO KANAUCHI, HIDEO SHIIKI, and KAZUHIRO DOHI

Pirfenidon – TGF β inhibitörü

- TGF-β inhibitörü ⇨ Antifibrotik
- Anti-TNF etkinliğe sahip ⇨ Antiinflamatuar



NIH clinical research studies

Protocol Number: 05-DK-0113

Active Follow-up, Protocols NOT Recruiting New Patients

Title: Pirfenidone: A Novel Anti-Scarring Therapy for Advanced Diabetic Nephropathy

Number: 05-DK-0113

Summary: This study will determine whether the experimental drug pirfenidone can slow kidney disease in patients with diabetes. Diabetes can cause accumulation of proteins in the kidneys, leading to scar formation and eventual kidney failure. Pirfenidone has been beneficial in other diseases involving scar formation, such as pulmonary fibrosis and focal segmental glomerulosclerosis. The drug may be able to slow scar formation in diabetic kidney disease as well, possibly prolonging kidney function.

Patients 18 years of age and older with type 1 or 2 diabetes who have increased protein leakage in their urine, whose blood pressure and blood sugar are well controlled, and who are taking ACE inhibitors or angiotensin receptor blockers may be eligible for this

Pirfenidon Denemeleri

Akciğer Fibrozisini Önleme Çalışmaları

- İdiyopatik AC fibrozisi olan hastalarda
  - Solunum fonksiyonlarını daha iyi korumuştur

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 159 1999

Treatment of Idiopathic Pulmonary Fibrosis with a New Antifibrotic Agent, Pirfenidone

Results of a Prospective, Open-label Phase II Study

GANESH RAGHU, W. CRAIG JOHNSON, DIANE LOCKHART, and YOLANDA MAGETO

University of Washington, and Statistics and Epidemiology Research Corporation, Seattle, Washington

Idiopathic pulmonary fibrosis (IPF) is a progressive clinical syndrome of unknown etiology and fatal outcome. Currently available therapies are ineffective and associated with significant adverse effects. Pirfenidone, a new, investigational antifibrotic agent, was evaluated for its tolerability and usefulness in terminally ill patients with advanced IPF. Consecutive patients with IPF and deterioration despite conventional therapy or who were unable to tolerate or unwilling to try conventional therapy were treated with oral pirfenidone. Treatment was administered on a compassionate basis (open-label). Fifty-four patients were followed for mortality, change in lung function, and adverse effects. Their mean age was 62, mean duration of symptoms 4.6 yr, and time since lung biopsy was 3.2 yr. Conven-

Pirfenidon Denemeleri

Deneysel Çalışmalar

- Diyabetik modellerde:
  - Renal fibrozisi önlüyor
  - Kardiyak fibrozisi önlüyor

British Journal of Pharmacology (2001) 133, 687–694

www.nature.com/bjp

Reversal of cardiac and renal fibrosis by pirfenidone and spironolactone in streptozotocin-diabetic rats

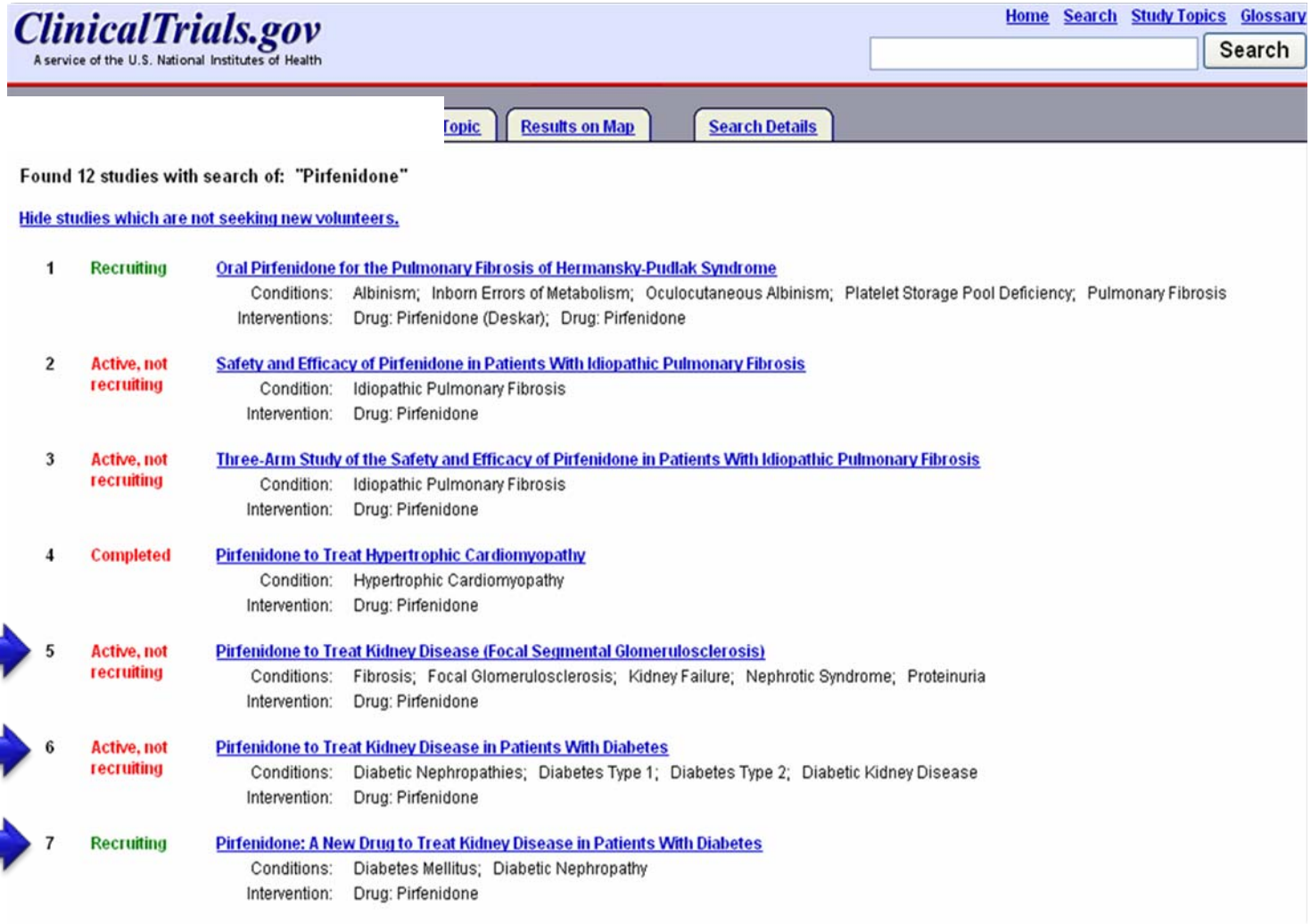
[1]Goran Miric, [2]Catherine Dallemagne, [3]Zoltan Endre, [4]Solomon Margolin, [1]Stephen M. Taylor & *,[1]Lindsay Brown

[1]Department of Physiology and Pharmacology, School of Biomedical Sciences, The University of Queensland, Australia; [2]School of Life Science, Queensland University of Technology, Australia; [3]Department of Medicine, The University of Queensland, Australia and [4]Marnac Inc, Dallas, Texas, U.S.A.

1 Fibrosis leads to chronic impairment of cardiac and renal function and thus reversal of existing fibrosis may improve function and survival. This project has determined whether pirfenidone, a new antifibrotic compound, and spironolactone, an aldosterone antagonist, reverse both deposition of the major extracellular matrix proteins, collagen and fibronectin, and functional changes in the streptozotocin(STZ)-diabetic rat.

Pirfenidon Denemeleri

Klinik Çalışmalar



ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Home Search Study Topics Glossary

Search

Topic | Results on Map | Search Details

Found 12 studies with search of: "Pirfenidone"

Hide studies which are not seeking new volunteers.

1 Recruiting — Oral Pirfenidone for the Pulmonary Fibrosis of Hermansky-Pudlak Syndrome
Conditions: Albinism; Inborn Errors of Metabolism; Oculocutaneous Albinism; Platelet Storage Pool Deficiency; Pulmonary Fibrosis
Interventions: Drug: Pirfenidone (Deskar); Drug: Pirfenidone

2 Active, not recruiting — Safety and Efficacy of Pirfenidone in Patients With Idiopathic Pulmonary Fibrosis
Condition: Idiopathic Pulmonary Fibrosis
Intervention: Drug: Pirfenidone

3 Active, not recruiting — Three-Arm Study of the Safety and Efficacy of Pirfenidone in Patients With Idiopathic Pulmonary Fibrosis
Condition: Idiopathic Pulmonary Fibrosis
Intervention: Drug: Pirfenidone

4 Completed — Pirfenidone to Treat Hypertrophic Cardiomyopathy
Condition: Hypertrophic Cardiomyopathy
Intervention: Drug: Pirfenidone

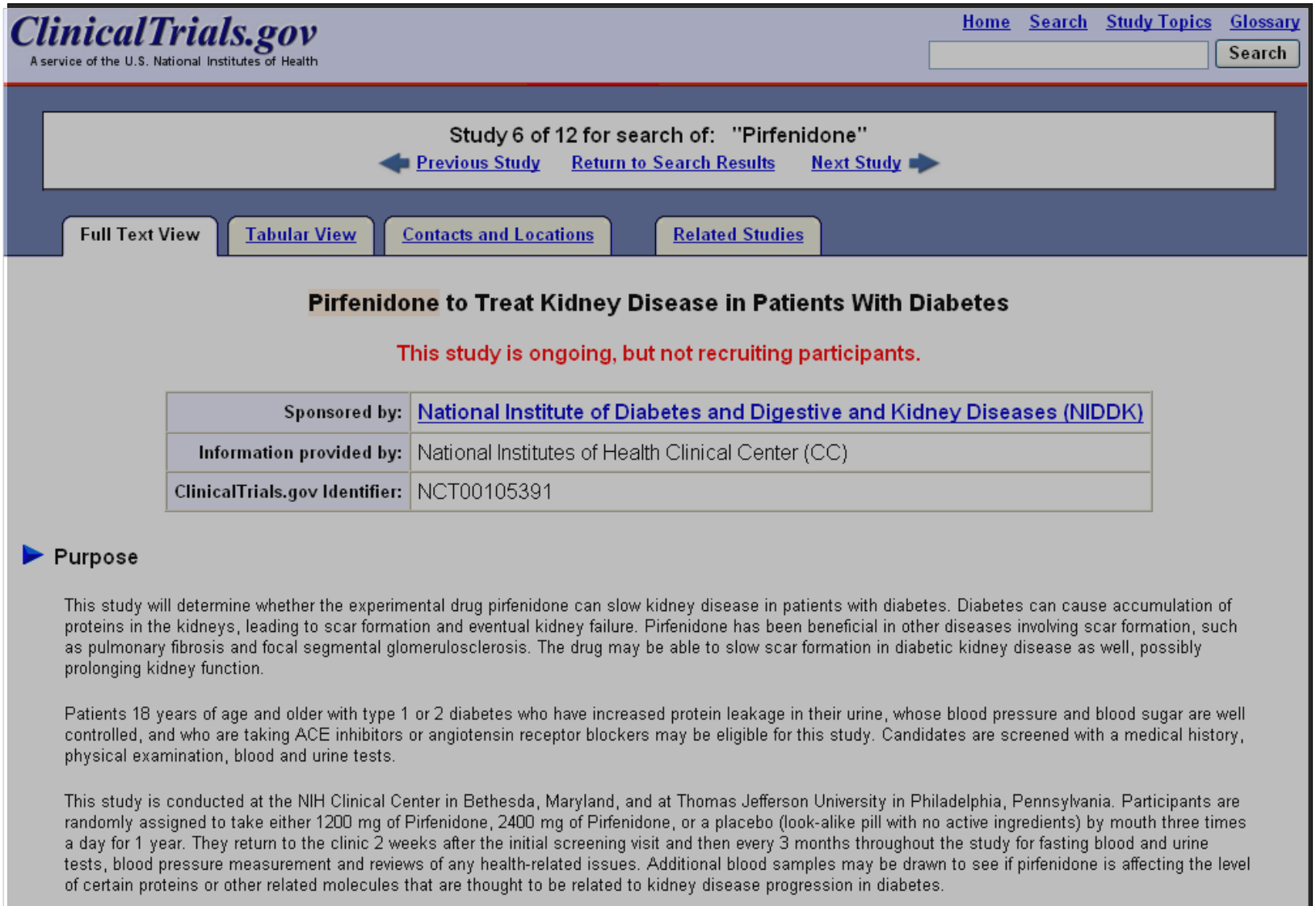
5 Active, not recruiting — Pirfenidone to Treat Kidney Disease (Focal Segmental Glomerulosclerosis)
Conditions: Fibrosis; Focal Glomerulosclerosis; Kidney Failure; Nephrotic Syndrome; Proteinuria
Intervention: Drug: Pirfenidone

6 Active, not recruiting — Pirfenidone to Treat Kidney Disease in Patients With Diabetes
Conditions: Diabetic Nephropathies; Diabetes Type 1; Diabetes Type 2; Diabetic Kidney Disease
Intervention: Drug: Pirfenidone

7 Recruiting — Pirfenidone: A New Drug to Treat Kidney Disease in Patients With Diabetes
Conditions: Diabetes Mellitus; Diabetic Nephropathy
Intervention: Drug: Pirfenidone

Pirfenidon Denemeleri

Klinik Çalışmalar



ClinicalTrials.gov
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Home Search Study Topics Glossary

Search

Study 6 of 12 for search of: "Pirfenidone"

Previous Study Return to Search Results Next Study

Full Text View | Tabular View | Contacts and Locations | Related Studies

Pirfenidone to Treat Kidney Disease in Patients With Diabetes

This study is ongoing, but not recruiting participants.

Sponsored by:	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Information provided by:	National Institutes of Health Clinical Center (CC)
ClinicalTrials.gov Identifier:	NCT00105391

Purpose

This study will determine whether the experimental drug pirfenidone can slow kidney disease in patients with diabetes. Diabetes can cause accumulation of proteins in the kidneys, leading to scar formation and eventual kidney failure. Pirfenidone has been beneficial in other diseases involving scar formation, such as pulmonary fibrosis and focal segmental glomerulosclerosis. The drug may be able to slow scar formation in diabetic kidney disease as well, possibly prolonging kidney function.

Patients 18 years of age and older with type 1 or 2 diabetes who have increased protein leakage in their urine, whose blood pressure and blood sugar are well controlled, and who are taking ACE inhibitors or angiotensin receptor blockers may be eligible for this study. Candidates are screened with a medical history, physical examination, blood and urine tests.

This study is conducted at the NIH Clinical Center in Bethesda, Maryland, and at Thomas Jefferson University in Philadelphia, Pennsylvania. Participants are randomly assigned to take either 1200 mg of Pirfenidone, 2400 mg of Pirfenidone, or a placebo (look-alike pill with no active ingredients) by mouth three times a day for 1 year. They return to the clinic 2 weeks after the initial screening visit and then every 3 months throughout the study for fasting blood and urine tests, blood pressure measurement and reviews of any health-related issues. Additional blood samples may be drawn to see if pirfenidone is affecting the level of certain proteins or other related molecules that are thought to be related to kidney disease progression in diabetes.

Pirfenidon Denemeleri

Klinik Çalışmalar

ClinicalTrials.gov
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Home Search Study Topics Glossary

Search

Study 7 of 12 for search of: "Pirfenidone"

Previous Study Return to Search Results Next Study

Full Text View | Tabular View | Contacts and Locations | Related Studies

Pirfenidone: A New Drug to Treat Kidney Disease in Patients With Diabetes

This study is currently recruiting participants.
Verified by Sharma, Kumar, M.D., June 2006

Sponsors and Collaborators:	**Sharma, Kumar, M.D.** National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Information provided by:	Sharma, Kumar, M.D.
ClinicalTrials.gov Identifier:	NCT00063583

Purpose

The purpose of this study is to determine whether a new investigational drug, pirfenidone, will be an effective therapy for diabetic patients with kidney dysfunction. Our hypothesis is that administration of pirfenidone to type 1 and type 2 diabetic patients with advanced kidney disease will lead to preservation of kidney function.

Condition	Intervention	Phase
Diabetes Mellitus Diabetic Nephropathy	Drug: **Pirfenidone**	Phase I Phase II

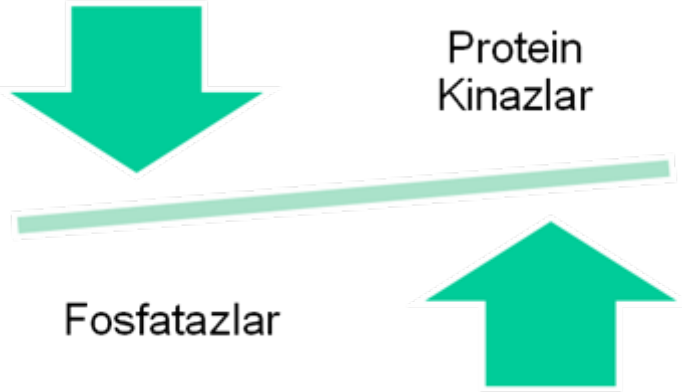
Diyabetik Nefropati Tedavisi

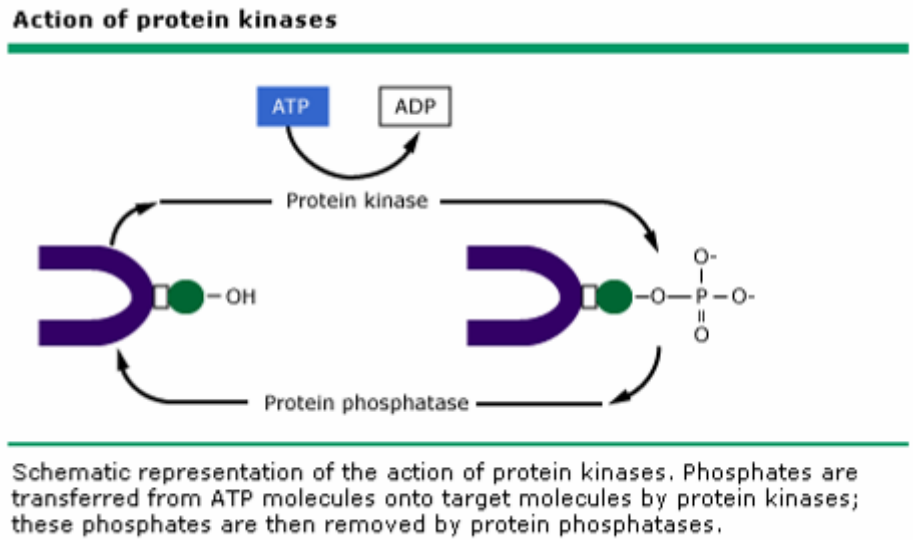
PKC İnhibisyonu

Protein Kinaz / Fosfataz Dengesi

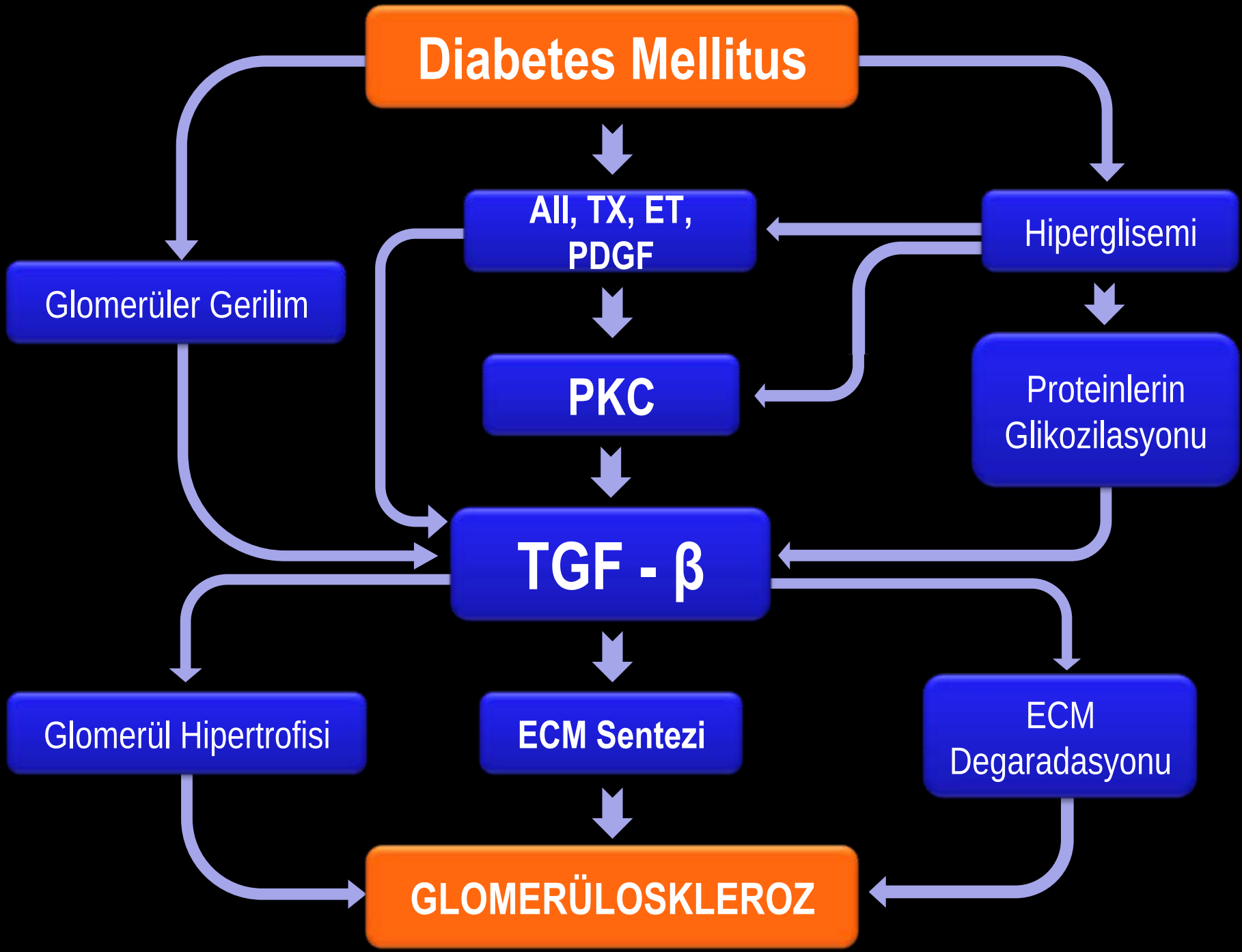
Hücre Faaliyetlerinin Düzenlenmesi

- Enzimler
- Reseptörler
- İyon kanalları
- …





Schematic representation of the action of protein kinases. Phosphates are transferred from ATP molecules onto target molecules by protein kinases; these phosphates are then removed by protein phosphatases.


Diabetes Mellitus
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Proteinlerin Glikozilasyonu
TGF - β
Glomerül Hipertrofisi
ECM Sentezi
ECM Degaradasyonu
GLOMERÜLOSKLEROZ

PKC'nin Diyabetik Nefropatide Rolü

- Diyabetik rat glomerüllerinde PKC aktivasyonu yüksek

Protein Kinase C Is Activated in Glomeruli from Streptozotocin Diabetic Rats

Possible Mediation by Glucose

Patricia A. Craven and Frederick R. DeRubertis
Department of Medicine, Veterans Administration Medical Center and University of Pittsburgh, Pittsburgh, Pennsylvania 15240

J Clin Invest. 1989 May; 83(5): 1667–1675.

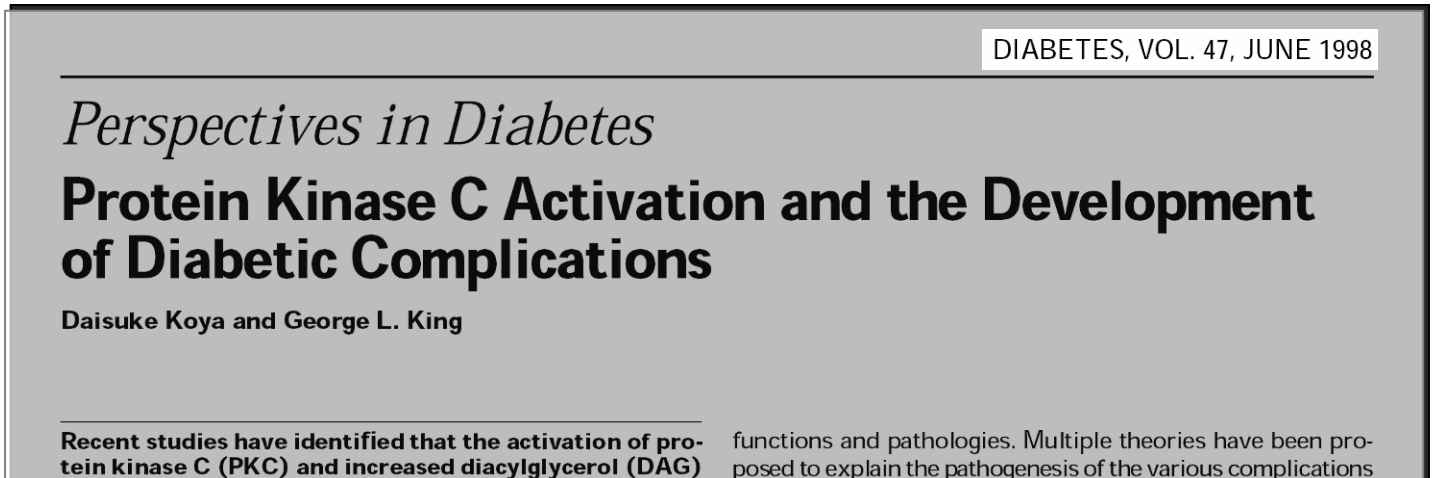
Abstract

Glomerular inositol content and the turnover of polyphosphoinositides was reduced by 58% in 1–2 wk streptozotocin diabetic rats. Addition of inositol to the incubation medium increased polyphosphoinositide turnover in glomeruli from diabetic rats to control values. Despite the reduction in inositol content and polyphosphoinositide turnover, protein kinase C was activated in glomeruli from diabetic rats, as assessed by an increase in the percentage of enzyme activity associated with the particulate cell fraction. Total protein kinase C activity was not different between glomeruli from control and diabetic rats. Treatment of diabetic rats with insulin to achieve near euglycemia prevented the increase in particulate protein kinase C. Moreover, incubation of glomeruli from control rats with glucose (100–1,000 mg/dl) resulted in a progressive increase in

nase C. Impaired diacylglycerol availability in turn could lead to the impaired activation of protein kinase C. It has been speculated that reduced protein kinase C activity may contribute to the development of diabetic complications including nephropathy (2). Some (12) but not all (13, 14) studies support this notion. With respect to the renal glomerulus, inositol content was reported to be reduced in the streptozotocin diabetic rat (5). However, the impact of reduced inositol content on inositol phospholipid turnover and the state of activation of protein kinase C in glomeruli has not been examined. Accordingly, in the present study we examined (*a*) inositol content; (*b*) the turnover of labeled inositol phospholipids; and (*c*) the state of activation of protein kinase C in glomeruli isolated from rat kidneys 1–2 wk after induction of diabetes with streptozotocin. The results demonstrate that protein kinase C is activated in glomeruli from diabetic rats despite a reduction

PKC Aktivasyonu
Diyabetik Komplikasyonlar

- Hiperglisemi hücre-içi DAG düzeyini yükseltiyor..
- DAG düzeyinin yükselmesi PKC'yi etkinleştiriyor..
- PKC'nin aşırı aktivasyonu diabetik komplikasyonlara yol açıyor…



DIABETES, VOL. 47, JUNE 1998

Perspectives in Diabetes

Protein Kinase C Activation and the Development of Diabetic Complications

Daisuke Koya and George L. King

Recent studies have identified that the activation of protein kinase C (PKC) and increased diacylglycerol (DAG)

functions and pathologies. Multiple theories have been proposed to explain the pathogenesis of the various complications

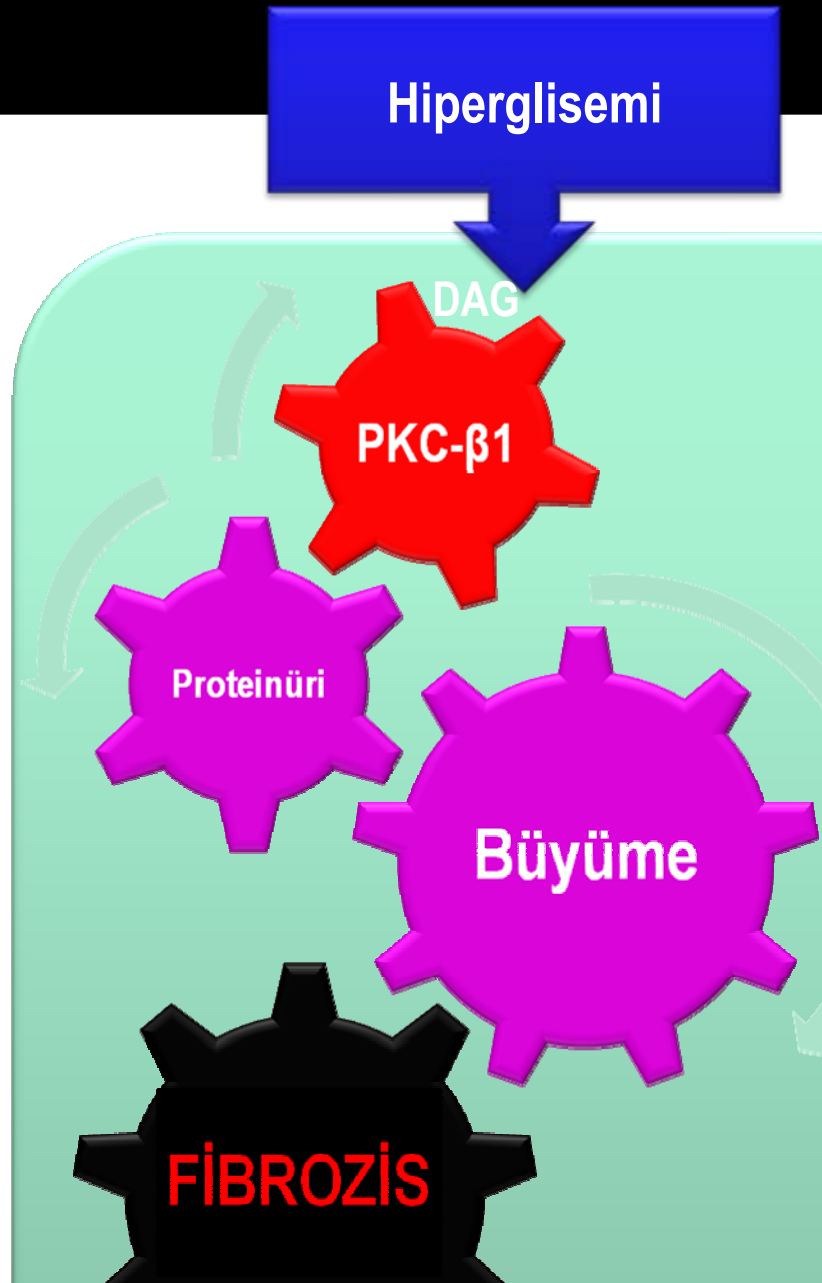
Diyabetik Ortam

Protein kinaz C β1 (PKC-β1)

DAG ve PKC aktivitesi artınca:

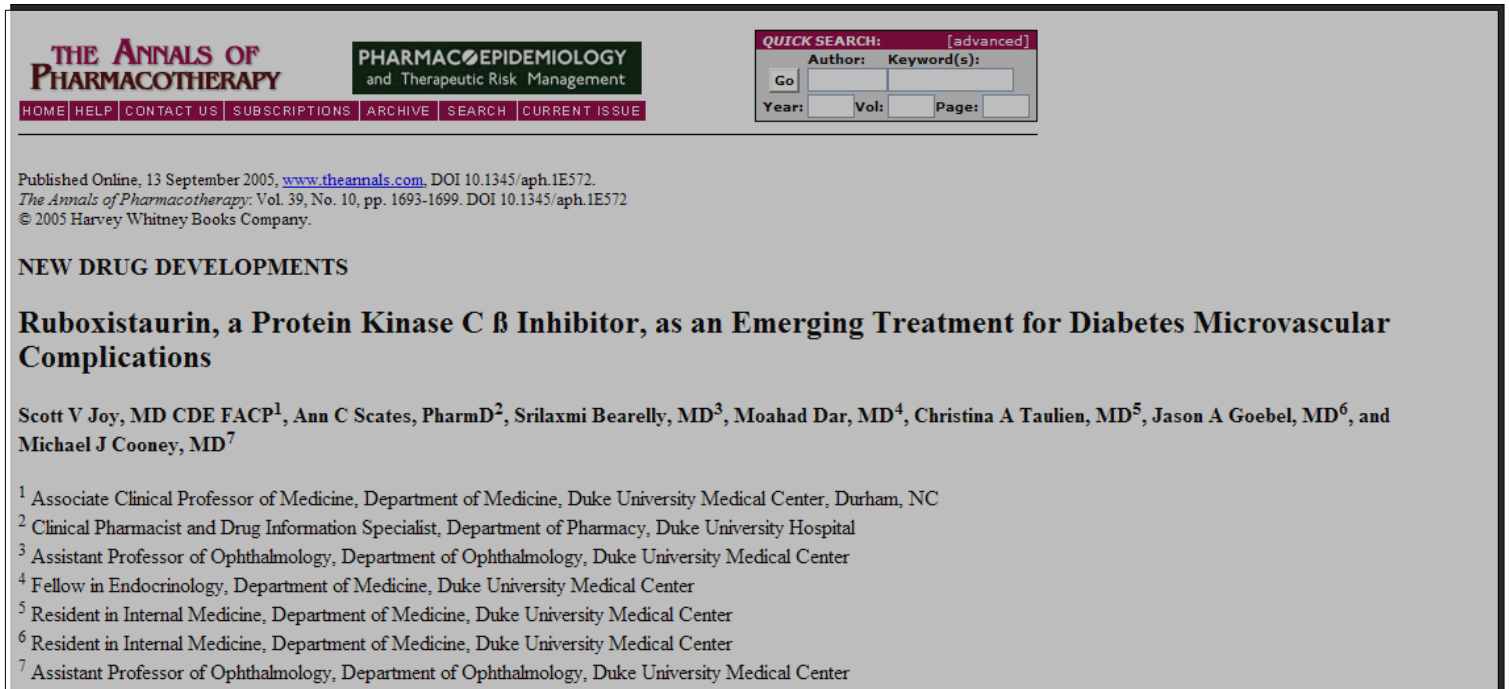
- Vasküler düz kas değişiklikleri
- Endotel permeabilite değişiklikleri
- Gen ekspresyonu değişiklikleri

Tipik damar lezyonları



PKC İnhibisyonu
Ruboxistaurin

- PKC-β1'in yüksek spesifik inhibitörü.



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Year: Vol: Page:

Published Online, 13 September 2005, www.theannals.com, DOI 10.1345/aph.1E572.
The Annals of Pharmacotherapy: Vol. 39, No. 10, pp. 1693-1699. DOI 10.1345/aph.1E572

NEW DRUG DEVELOPMENTS

Ruboxistaurin, a Protein Kinase C ß Inhibitor, as an Emerging Treatment for Diabetes Microvascular Complications

Scott V Joy, MD CDE FACP[1], Ann C Scates, PharmD[2], Srilaxmi Bearelly, MD[3], Moahad Dar, MD[4], Christina A Taulien, MD[5], Jason A Goebel, MD[6], and Michael J Cooney, MD[7]

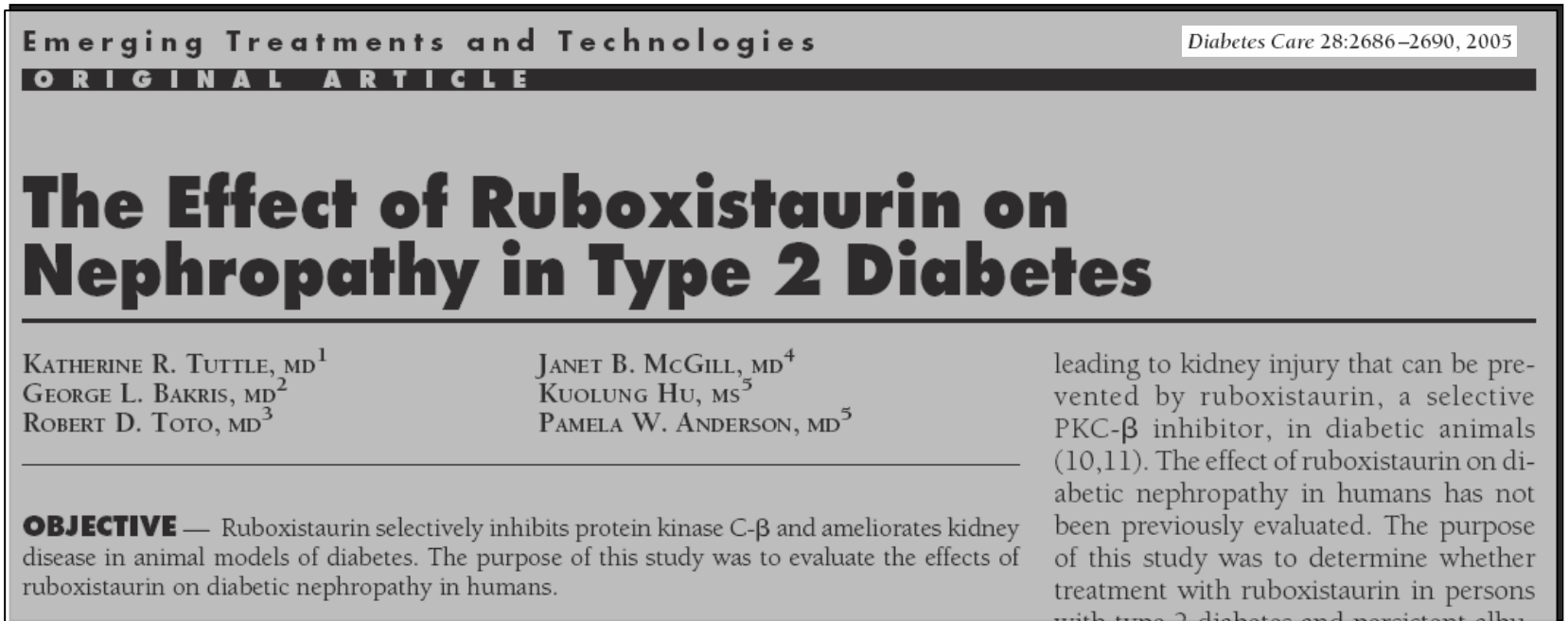
[1] Associate Clinical Professor of Medicine, Department of Medicine, Duke University Medical Center, Durham, NC
[2] Clinical Pharmacist and Drug Information Specialist, Department of Pharmacy, Duke University Hospital
[3] Assistant Professor of Ophthalmology, Department of Ophthalmology, Duke University Medical Center
[4] Fellow in Endocrinology, Department of Medicine, Duke University Medical Center
[5] Resident in Internal Medicine, Department of Medicine, Duke University Medical Center
[6] Resident in Internal Medicine, Department of Medicine, Duke University Medical Center
[7] Assistant Professor of Ophthalmology, Department of Ophthalmology, Duke University Medical Center

Ruboxistaurin

- Diyabetik ve hipertansif nefropati hayvan modellerinde etkili…
- PKC-β1'e bağlı olumsuz etkileri hafifletiyor:
  - GFR'de restorasyon,
  - Albüminüride azalma,
  - Prefibrotik matriks proteinlerinde azalma sağlıyor..

Ruboxistaurin
Diyabetik Nefropati

- Tasarım : Randomize, çift-kör, plasebo kontrollü deneme
- Hastalar : Tip 2 diyabetik ve proteinürik 123 kişi
- İlaç : Ruboxistaurin 32 mg/gün
- Süre : 1 yıl
- Son Nokta : Albümin / kreatinin oranında değişim, GFR'de değişim



Emerging Treatments and Technologies
ORIGINAL ARTICLE
Diabetes Care 28:2686–2690, 2005

The Effect of Ruboxistaurin on Nephropathy in Type 2 Diabetes

KATHERINE R. TUTTLE, MD[1]
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ROBERT D. TOTO, MD[3]
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KUOLUNG HU, MS[5]
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OBJECTIVE — Ruboxistaurin selectively inhibits protein kinase C-β and ameliorates kidney disease in animal models of diabetes. The purpose of this study was to evaluate the effects of ruboxistaurin on diabetic nephropathy in humans.

leading to kidney injury that can be prevented by ruboxistaurin, a selective PKC-β inhibitor, in diabetic animals (10,11). The effect of ruboxistaurin on diabetic nephropathy in humans has not been previously evaluated. The purpose of this study was to determine whether treatment with ruboxistaurin in persons

Ruboxistaurin
Diyabetik Nefropati

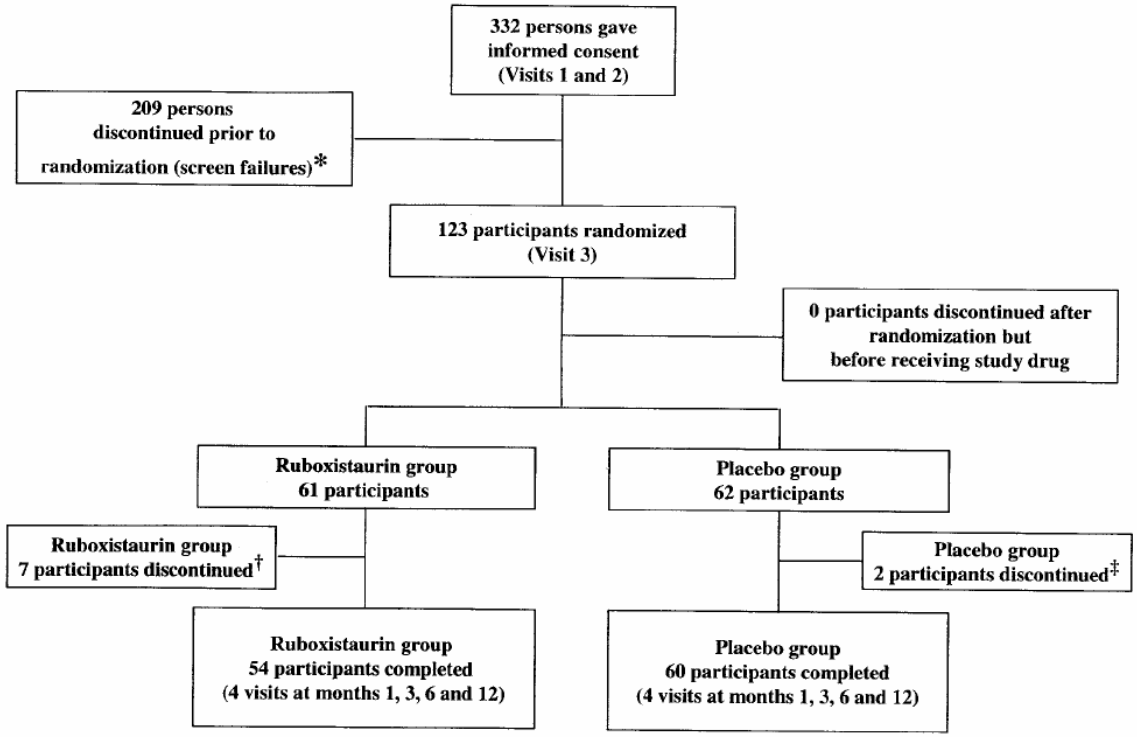


Figure 1—*Disposition of persons who gave informed consent and participants who were randomized. *Reasons for screen failure: ACR too low (n = 146), serum creatinine too high (n = 17), ACR too high (n = 15), ACR too variable (n = 9), A1C too high (n = 8), mean arterial blood pressure >110 mmHg (n = 1), or miscellaneous other (n = 13). †Reasons for discontinuation in the ruboxistaurin group: metastatic cancer of unknown primary origin (n = 1), libido decreased (n = 1), mental status changes (n = 1), or personal conflict (n = 4). ‡Reasons for discontinuation in the placebo group: personal conflict (n = 2).*

Ruboxistaurin
Diyabetik Nefropati

Table 2—*Medication use at baseline*

	Placebo	RBX	All	*P* value
n	62	61	123	
Insulin	48 (77)	44 (72)	92 (75)	0.539
Lipid-lowering drugs	43 (69)	38 (62)	81 (66)	0.451
Statin	43 (69)	36 (59)	79 (64)	0.262
Fibrate	7 (11)	4 (7)	11 (9)	0.530
ACE inhibitor	46 (74)	44 (72)	90 (73)	0.841
ARB	28 (45)	23 (38)	51 (42)	0.466
Both ACE inhibitor and ARB	12 (19)	6 (10)	18 (15)	0.202
Calcium channel blockers	33 (53)	26 (43)	59 (48)	0.281
Nondihydropyridine	10 (16)	4 (7)	14 (11)	0.154
Dihydropyridine	23 (37)	23 (38)	46 (37)	0.999
Diuretics	40 (65)	33 (54)	73 (59)	0.274
β-Blocker	26 (42)	21 (34)	47 (38)	0.459
Other antihypertensive agents	11 (18)	16 (26)	27 (22)	0.283
Antihypertensive agents taken per participant (*n*)	4.1 ± 1.5	3.6 ± 2.0	3.9 ± 1.8	0.052

Data are *n* (%) or means ± SD. RBX, 32 mg/day ruboxistaurin.

Ruboxistaurin
Diyabetik Nefropati

Table 3—*Change from baseline in urinary ACR and eGFR, blood pressure, and A1C at follow-up visits*

Treatment	*n*	1 month	3 months	6 months	12 months
Urinary ACR change (%)*					
Placebo	62	−16 ± 7†	−9 ± 8	−9 ± 10	−9 ± 11
RBX	59	−24 ± 7†	−28 ± 6†	−29 ± 8†	−24 ± 9†
Urinary ACR change (mg/g)‡					
Placebo	62	17 (424)	−37 (413)†	21 (661)	26 (896)†
RBX	59	−60 (363)†§	−139 (417)†§	−136 (598)	−121 (481)
eGFR change (ml/min per 1.73 m^2)					
Placebo	62	—	—	−2.7 ± 1.8	−4.8 ± 1.8†
RBX	57	—	—	−0.2 ± 1.9	−2.5 ± 1.9
Systolic blood pressure (mmHg)					
Placebo	62	135 ± 16	135 ± 15	136 ± 16	138 ± 19
RBX	59	135 ± 15	136 ± 15	134 ± 16	134 ± 18
Diastolic blood pressure (mmHg)					
Placebo	62	77 ± 12	76 ± 8	76 ± 10	76 ± 10
RBX	59	74 ± 10	74 ± 9	73 ± 11	74 ± 10
A1C (%)					
Placebo	62	—	—	7.7 ± 1.1	7.7 ± 1.2
RBX	56	—	—	8.0 ± 1.3	7.9 ± 1.3

Data are means ± SD unless otherwise indicated. *ACR change from baseline (%) was calculated from log-transformed values using the ANCOVA model with least-square means (prespecified primary outcome). †Change from baseline, $P < 0.05$. ‡ACR change from baseline (mg/g) without log transformation reported as median (interquartile range for the middle two quartiles). §Difference between groups, $P < 0.05$. RBX, 32 mg/day ruboxistaurin.

Ruboxistaurin ve TGF-β

Preklinik Çalışmalar

- Ruboxistaurin TGF- β'nın aşırı ekspresyonunu azaltıyor..

Protein Kinase Cβ Inhibition Attenuates Osteopontin Expression, Macrophage Recruitment, and Tubulointerstitial Injury in Advanced Experimental Diabetic Nephropathy

Darren J. Kelly, Anna Chanty, Renae M. Gow, Yuan Zhang, and Richard E. Gilbert
Department of Medicine, University of Melbourne, St Vincent's Hospital, Fitzroy, Victoria, Australia

Tubulointerstitial macrophage accumulation is an important marker of prognosis that correlates closely with declining renal function in a range of human and experimental diseases, including diabetic nephropathy. These inflammatory cells are rich in the profibrotic growth factor TGF-β such that their presence in areas of injury is frequently associated with tissue fibrosis. The migration of macrophages occurs in response to the site-specific production of chemokines, with osteopontin closely associated with their trafficking into the tubulointerstitium of the kidney. Although cell culture studies indicate that protein kinase C (PKC) mediates the expression of osteopontin, its role in the *in vivo* setting is unknown. Accordingly, Ren-2 control and diabetic rats that were treated with or without the specific PKC-β isoform inhibitor ruboxistaurin (10 mg/kg per d) were examined. After 12 wk, diabetic rats showed increases in osteopontin expression in tubular epithelial cells of the cortex in association with macrophage infiltration, interstitial fibrosis, and activity of TGF-β as indicated by the expression of its receptor activated protein phospho-Smad2 ($P < 0.05$ for all parameters). Ruboxistaurin treatment significantly attenuated these parameters ($P < 0.05$) in diabetic rats without affecting either BP or glycemic control. These findings suggest that osteopontin and macrophage accumulation may play a role in the tubulointerstitial injury in diabetic nephropathy and that inhibition of osteopontin expression may be one of the mechanisms by which inhibition of the β-isoform of PKC confers a renoprotective effect.

J Am Soc Nephrol 16: 1654–1660, 2005. doi: 10.1681/ASN.2004070578

Ruboxistaurin ve TGF-β
Klinik Çalışmalar

- Prospektif, çift-kör, plasebo kontrollü klinik çalışma
- Hastalar: tip 2 diyabetik nefropatili olgular
- 32 mg/g Ruboksistaurin idrar TGF-β düzeyini etkiler mi?

Pathophysiology/Complications
BRIEF REPORT
DIABETES CARE, VOLUME 30, NUMBER 4, APRIL 2007

Effect of Ruboxistaurin on Urinary Transforming Growth Factor-β in Patients With Diabetic Nephropathy and Type 2 Diabetes

RICHARD E. GILBERT, MD, PHD[1,2]
SANDRA A. KIM, MD, MSC[1]
KATHERINE R. TUTTLE, MD[3]
GEORGE L. BAKRIS, MD[4]
ROBERT D. TOTO, MD[5]
JANET B. MCGILL, MD[6]
DOUGLAS J. HANEY, PHD[7]
DARREN J. KELLY, PHD[2]
PAMELA W. ANDERSON, MD[7]

Paired baseline and end point sample sets with sufficient urine (>2.0 ml) were available from 107 of 123 (87%) participants.

Before assay, 2.0 ml from each urine

Ruboxistaurin ve TGF-β

İdrar TGF-β/Kreatinin Oranı

- Her 2 grupta da artış var
- Plasebo: %43 artış (P<0.01)
- Ruboxistaurin: %19 artış (P: NS)

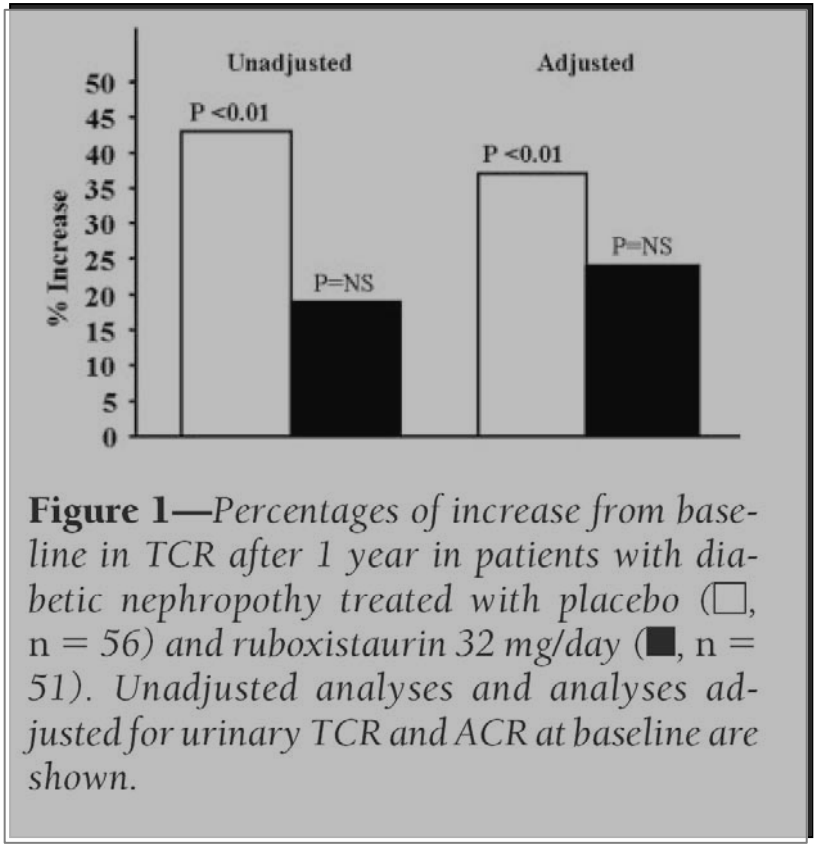


Figure 1—*Percentages of increase from baseline in TCR after 1 year in patients with diabetic nephropothy treated with placebo (□, n = 56) and ruboxistaurin 32 mg/day (■, n = 51). Unadjusted analyses and analyses adjusted for urinary TCR and ACR at baseline are shown.*

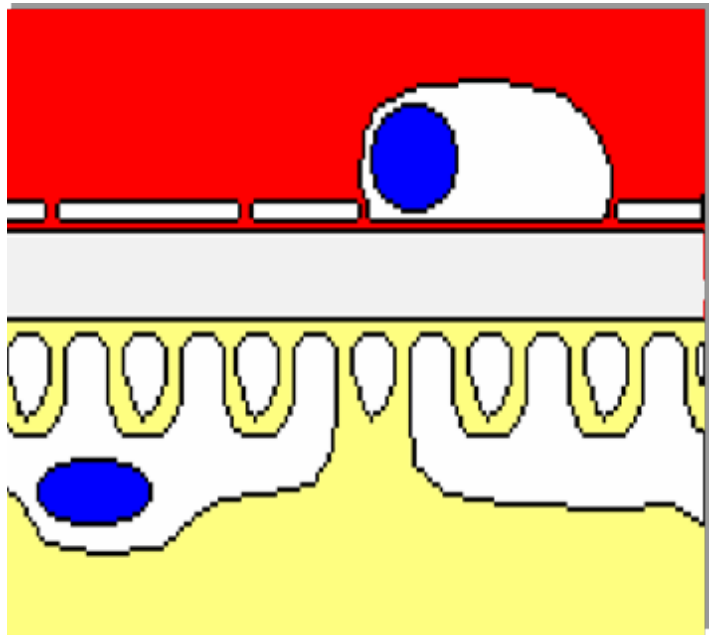
Diyabetik Nefropati Tedavisi

Bazal Membran Onarımı

Glomerüler Filtrasyon Katmanları

Elektriksel Yükler

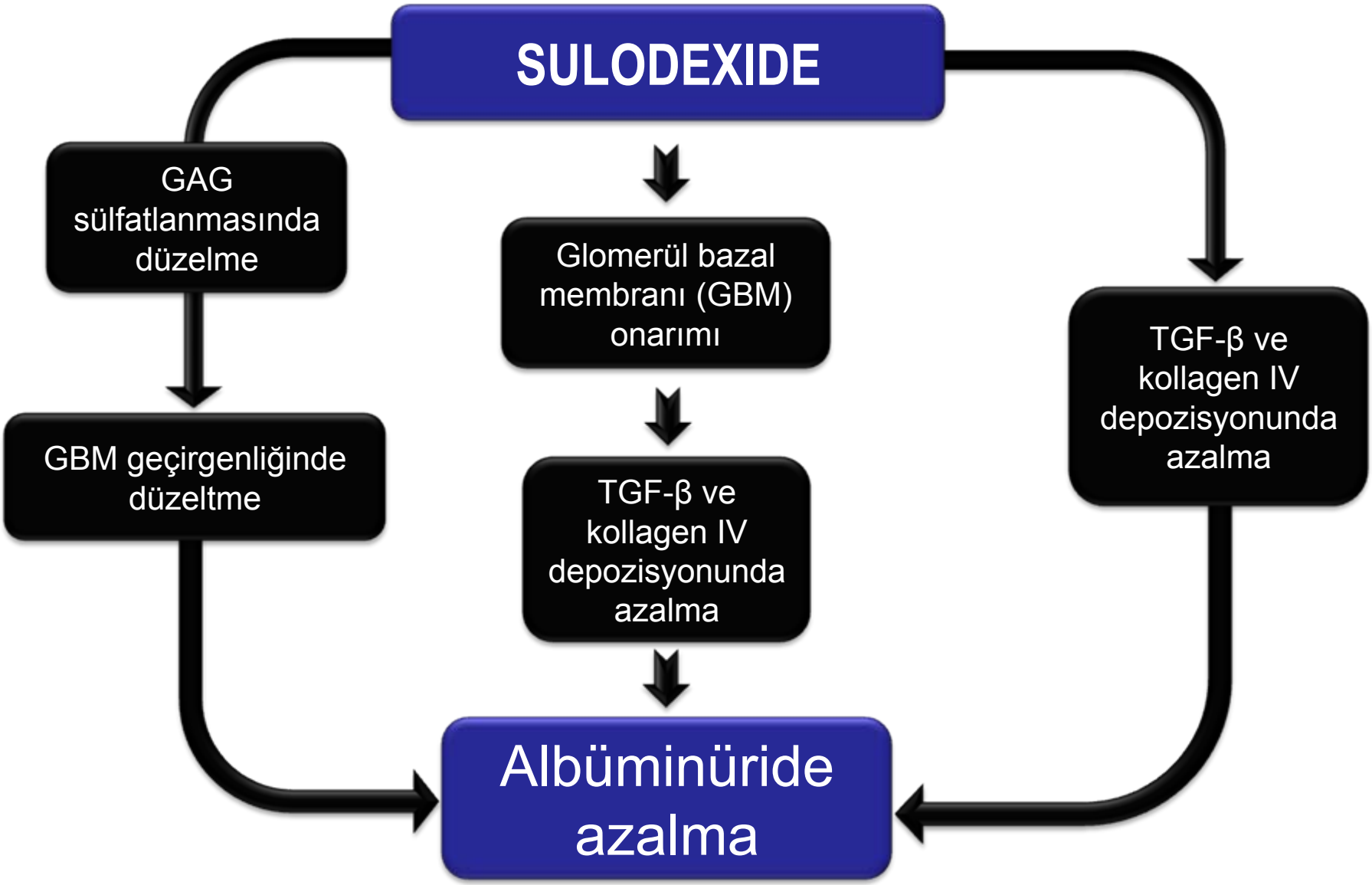
- Filtrasyon katmanları negatif yüklü bileşiklerle kaplı:
  - Sialoproteinler
  - Glikozaminoglikanlar (Ör: Heparan sülfat)



Bazal Membran Onarıcı Tedavi
Sulodexide

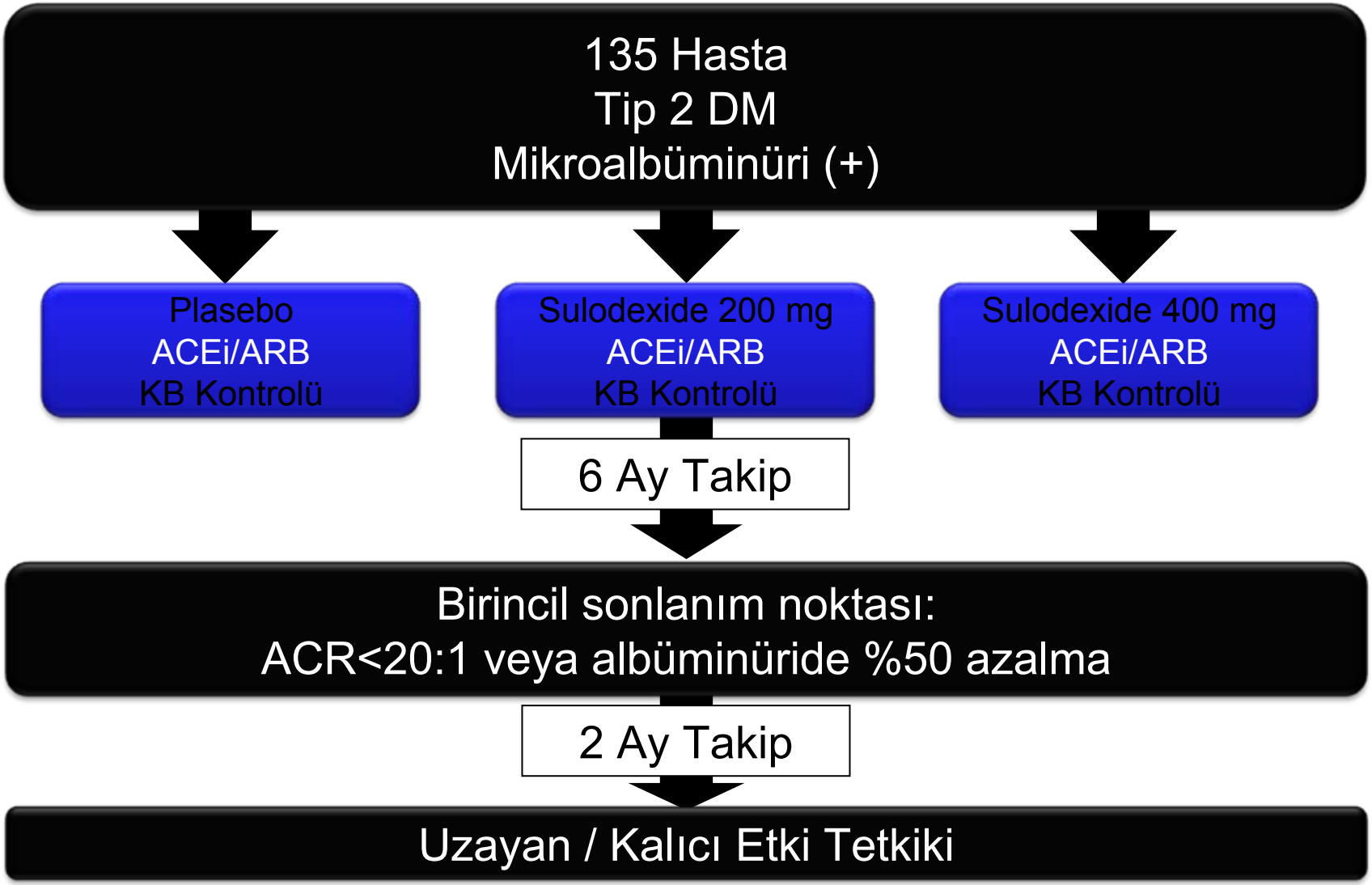
- Glikozaminoglikan sınıfı bir molekül
- Kompozisyon:
  - ‘Hızlı’ heparin (% 72-88)
  - Dermatan (% 12 - 28)
  - ‘Yavaş’ heparin (< % 4)
- Uygulama yolu: oral
- Oral alındığında antikoagülan etkinliği yok…

Etki Mekanizması



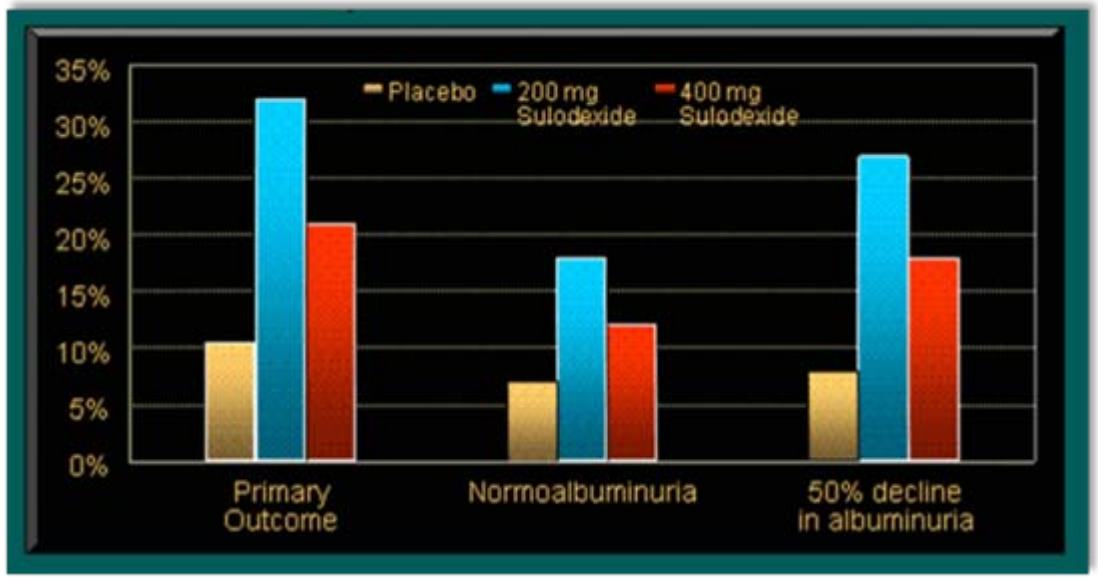
Sulodexide

Pilot Çalışma



Collaborative Study Group, ASN Renal Week 2005

Sulodexide
Pilot Çalışma



6. Ay

- Sulodexide kullanımı maksimum dozda ACEi / ARB alan hastalarda idrarla albümin atılım hızını düşürüyor…

Sulodexide

Klinik Denemeler

Oral Sulodexide Reduces Albuminuria in Microalbuminuric and Macroalbuminuric Type 1 and Type 2 Diabetic Patients: The Di.N.A.S. Randomized Trial

J Am Soc Nephrol 13: 1615–1625, 2002

Nephrol Dial Transplant (1997) 12: 2295–2300

Original Article

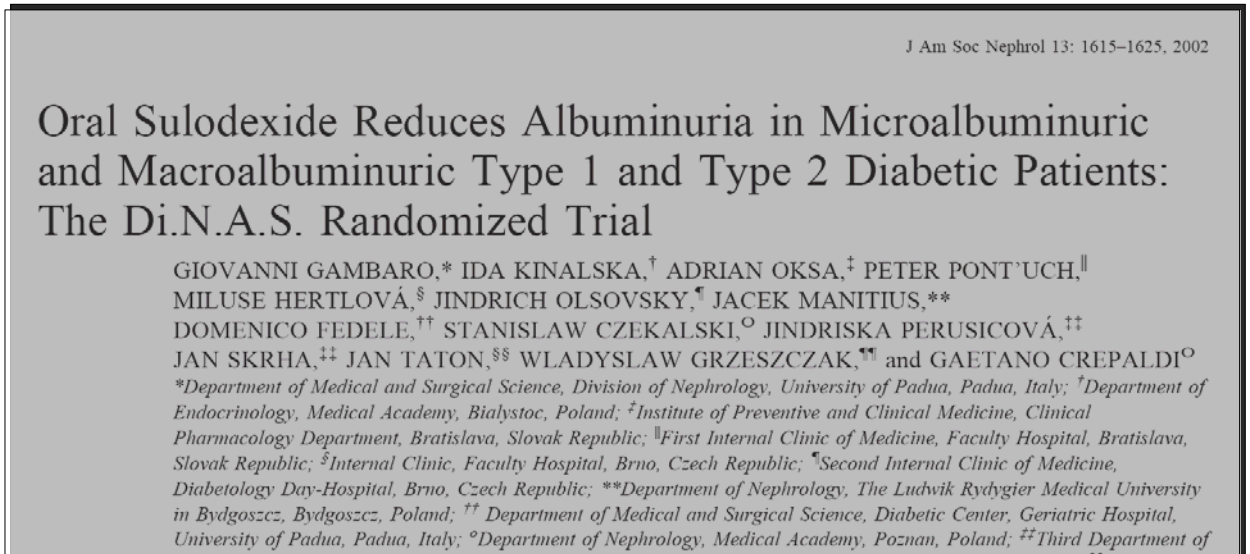
Nephrology Dialysis Transplantation

A randomized, controlled study of sulodexide therapy for the treatment of diabetic nephropathy

Sulodexide

Di.N.A.S. Denemesi

- Randomize çift-kör plasebo kontrollü deneme
- Hastalar:
  - Tip 1 ve Tip 2 DM
  - Mikroalbüminürik ve/veya makroalbüminürik



J Am Soc Nephrol 13: 1615–1625, 2002

Oral Sulodexide Reduces Albuminuria in Microalbuminuric and Macroalbuminuric Type 1 and Type 2 Diabetic Patients: The Di.N.A.S. Randomized Trial

GIOVANNI GAMBARO,* IDA KINALSKA,† ADRIAN OKSA,‡ PETER PONT'UCH,‖ MILUSE HERTLOVÁ,§ JINDRICH OLSOVSKY,¶ JACEK MANITIUS,** DOMENICO FEDELE,†† STANISLAW CZEKALSKI,° JINDRISKA PERUSICOVÁ,‡‡ JAN SKRHA,‡‡ JAN TATON,§§ WLADYSLAW GRZESZCZAK,¶¶ and GAETANO CREPALDI°

*Department of Medical and Surgical Science, Division of Nephrology, University of Padua, Padua, Italy; †Department of Endocrinology, Medical Academy, Bialystoc, Poland; ‡Institute of Preventive and Clinical Medicine, Clinical Pharmacology Department, Bratislava, Slovak Republic; ‖First Internal Clinic of Medicine, Faculty Hospital, Bratislava, Slovak Republic; §Internal Clinic, Faculty Hospital, Brno, Czech Republic; ¶Second Internal Clinic of Medicine, Diabetology Day-Hospital, Brno, Czech Republic; **Department of Nephrology, The Ludwik Rydygier Medical University in Bydgoszcz, Bydgoszcz, Poland; †† Department of Medical and Surgical Science, Diabetic Center, Geriatric Hospital, University of Padua, Padua, Italy; °Department of Nephrology, Medical Academy, Poznan, Poland; ‡‡Third Department of

Sulodexide

Di.N.A.S. Denemesi

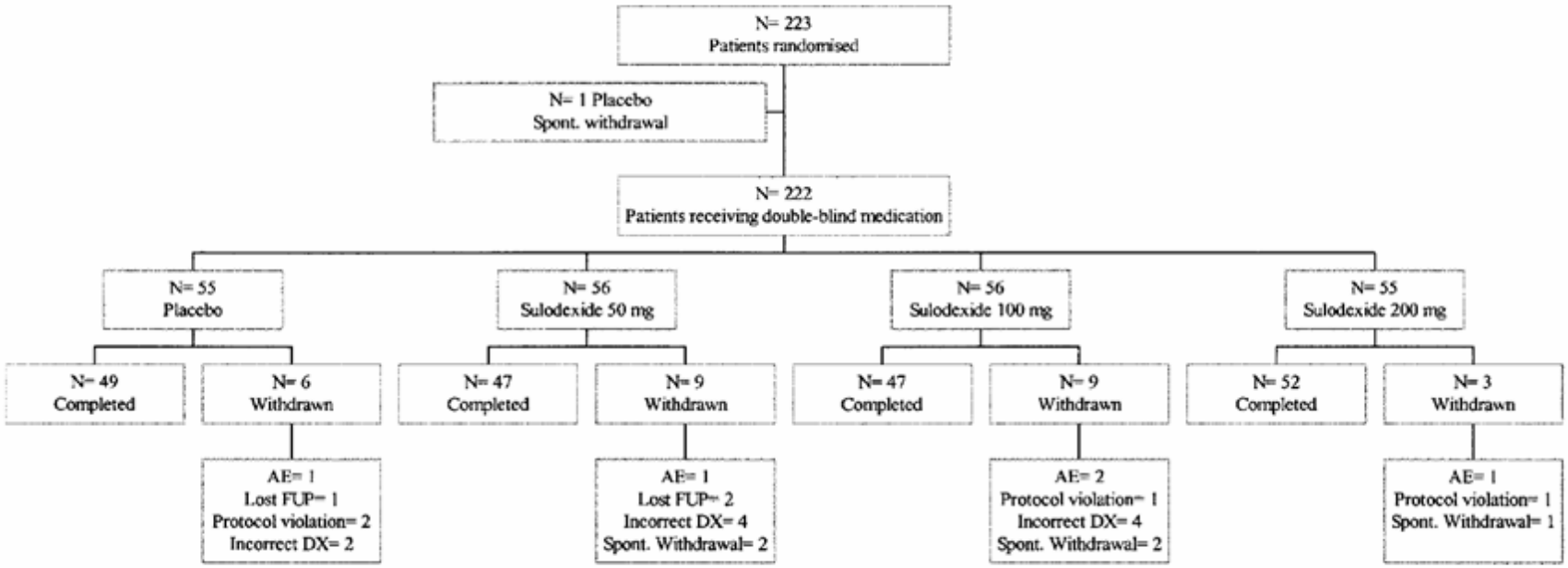


Figure 1. Disposition of patients. AE, adverse effect; DX, diagnosis; FUP, follow-up.

Sulodexide

Di.N.A.S. Denemesi

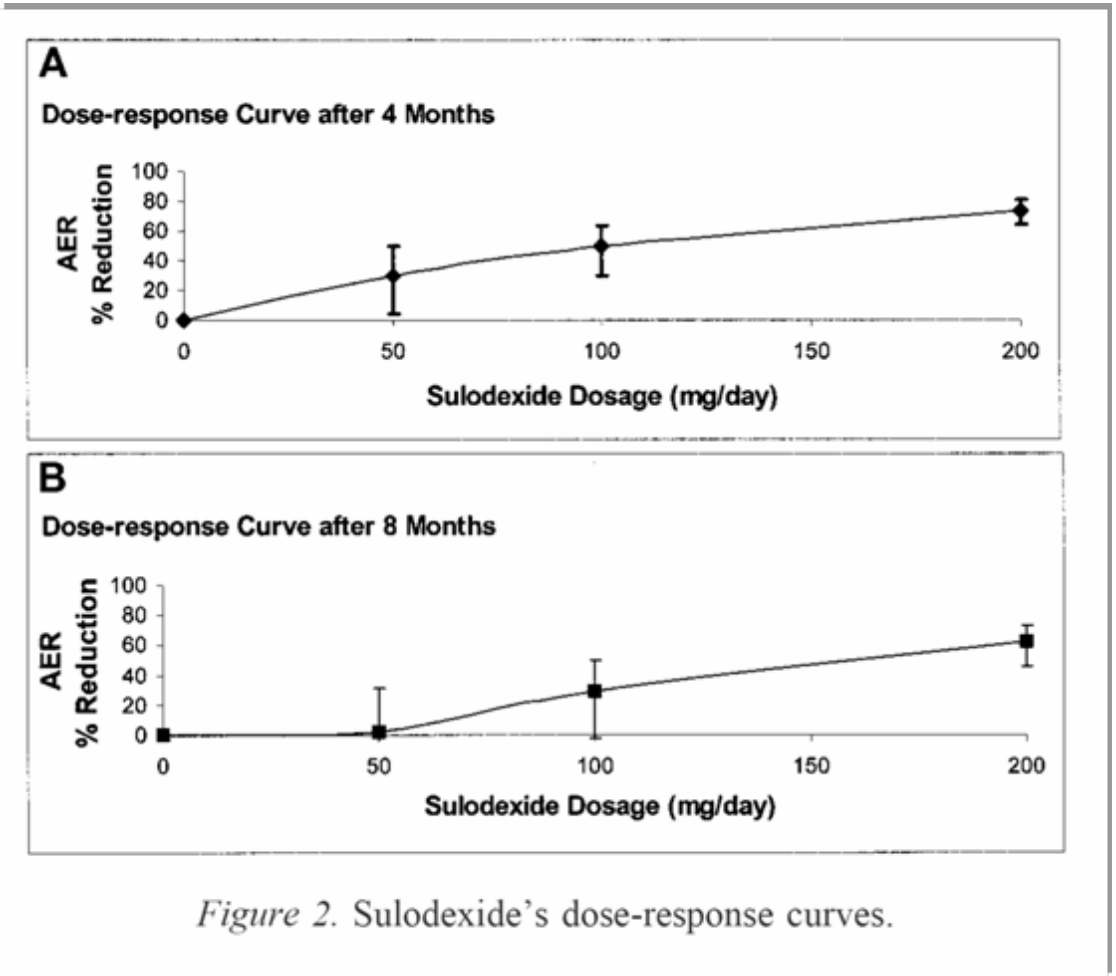


Figure 2. Sulodexide's dose-response curves.

Doz-cevap Eğrisi

Sulodexide

Di.N.A.S. Denemesi

Table 3. Effect of sulodexide on albumin excretion in the whole study group[a]

Group	Log AER			AER% Reduction (Efficacy Analysis)		AER% Reduction (Dose-Range Finding Analysis)	
	T0	T4	T8	T4 *versus* T0	T8 *versus* T0	T4 *versus* T4 Placebo	T8 *versus* T8 Placebo
Placebo	5.10 ± 0.19	5.31 ± 0.11	5.07 ± 0.13				
50 mg/d sulodexide	4.62 ± 0.16	4.95 ± 0.12	5.05 ± 0.13			30[b] (4 to 49)	
100 mg/d sulodexide	4.58 ± 0.17	4.63 ± 0.12	4.73 ± 0.13			49[c] (30 to 63)	
200 mg/d sulodexide	5.25 ± 0.18	3.98 ± 0.11	4.11 ± 0.13	43[d] (31 to 54)	30[d] (8 to 51)	74[c] (64 to 81)	62[c] (45 to 73)

[a] Values are log mean ± SEM or mean and confidence limits. AER, albumin excretion rate. Only statistical significant reductions are reported.
[b] $P < 0.03$.
[c] $P < 0.0001$ *versus* placebo.
[d] $P < 0.05$ *versus* T0.

Sulodexide'in Albümin Atılım Hızına Etkisi

Sulodexide
Devam eden araştırmalar

- Mikroalbüminürik hastalarda
  - Maksimum doz ACE veya ARB + Sulodexide
  - Birincil sonlanım noktası:
    - Normoalbüminemi veya AER'de %50 azalma

- Aşikar nefropati hastalarında
  - Birincil sonlanım noktası:
    - Serum kreatinin değerinin ikiye katlanması veya SDBY gelişmesi

Diyabetik Nefropati Tedavisi

PPAR Gamma Stimülasyonu

PPAR Gamma Stimülasyonu
Thiazolidinedionlar

DIABETES, VOL. 55, JUNE 2006

Original Article

Thiazolidinediones Ameliorate Diabetic Nephropathy via Cell Cycle–Dependent Mechanisms

Tatsuo Okada, Jun Wada, Kazuyuki Hida, Jun Eguchi, Izumi Hashimoto, Masako Baba, Akihiro Yasuhara, Kenichi Shikata, and Hirofumi Makino

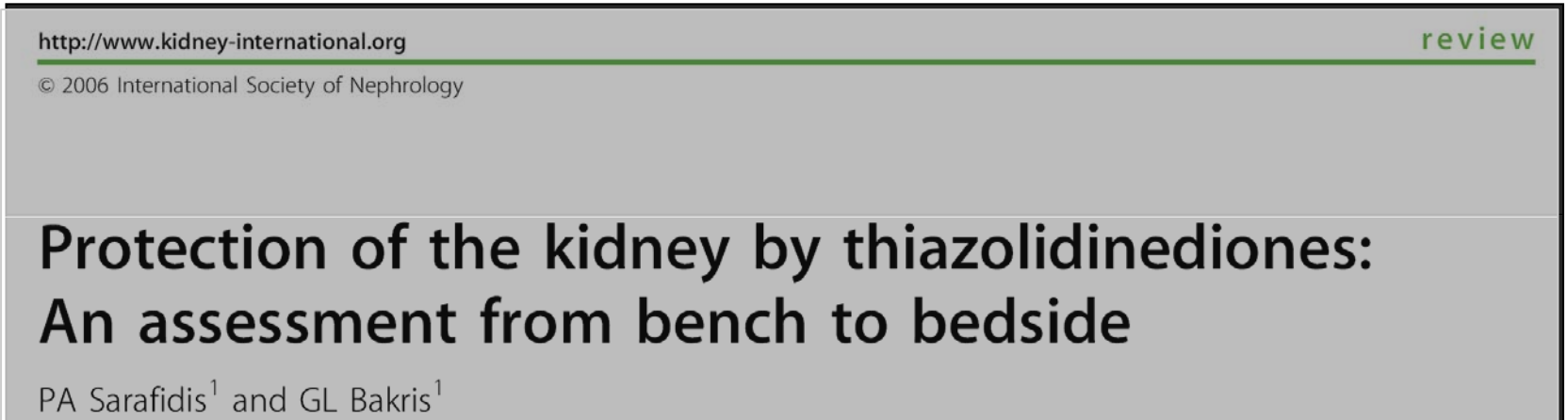
Thiazolidinediones are ligands for peroxisome proliferator–activated receptor (PPAR)-γ, widely used as insulin sensitizer in type 2 diabetic patients and implicated in apoptosis, cell proliferation, and cell cycle regulation. Here, the effect of thiazolidinediones on G1-phase cell cycle arrest, the hallmark in diabetic nephropathy, was investigated. Eight-week-old male Otsuka Long-Evans Tokushima fatty rats were treated with pioglitazone (1 mg · kg body wt^{-1} · day^{-1}) until 50 weeks of age and compared with insulin treatment. Although similar HbA_{1c} levels were observed in both groups, pioglitazone significantly inhibited glomerular hypertrophy and mesangial matrix expansion and reduced urinary albumin excretion compared with the insulin-treated group. In addition, pioglitazone significantly reduced the number of glomerular $p27^{Kip1}$-positive cells. Because prominent expression of PPAR-γ was observed in podocytes in glomeruli and cultured cells, conditionally immortalized mouse podocyte cells were cultured under 5.5 and 25 mmol/l D-glucose supplemented with

expressed in adipose tissues where it plays a role in lipid metabolism and adipogenesis and is also expressed in liver, skeletal muscle, intestine, colon, kidney, and cell types throughout the body, including monocytes and macrophages (3). The unsaturated fatty acids bind all three PPARs, whereas saturated fatty acids are poor PPAR ligands in general (4). The ligands for PPAR-γ include several prostanoids such as 15-deoxy-Δ (12,14)-prostaglandin J_2 and 15-hydroxy-eicosatetrenoic acid, metabolites of arachidonic acid (5,6). The pharmacological ligands for PPAR-γ are the thiozolidinediones (TZDs), which are widely used as an insulin sensitizer in type 2 diabetic patients and have been shown to possess potent anti-inflammatory and antineoplastic actions (1).

PPAR-γ expressed in adipocytes plays a pivotal role in adipocyte proliferation and differentiation, i.e., cell cycle regulation. After hormonal induction, growth-arrested

Thiazolidinedionlar (TZD)

- TZD'ler insülin direncini azaltır
- Etki mekanizması = PPAR Gamma stimülasyonu
- PPAR Gamma yağ dokusunda çok bulunur, ayrıca:
  - Damar düz kas hücreleri
  - Makrofajlar
  - Kolon epitel hücreleri
  - Glomerül ve tübül epitel hücrelerinde bulunuyor…


http://www.kidney-international.org review

Protection of the kidney by thiazolidinediones: An assessment from bench to bedside

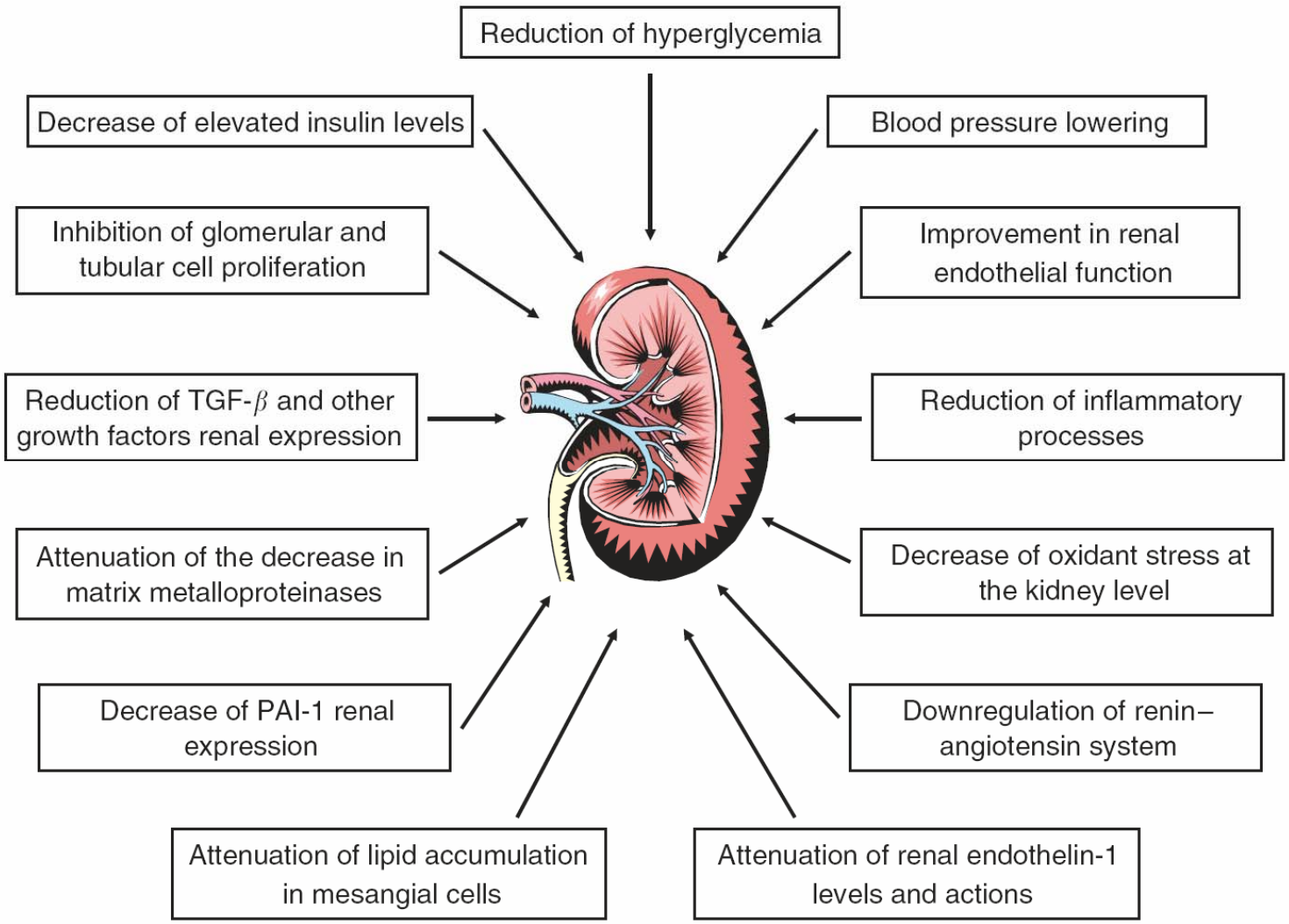
PA Sarafidis[1] and GL Bakris[1]

Thiazolidinedionlar (TZD)
Faydalı Etkiler

- Kan şekeri kontrolü
- Kan basıncı kontrolü
- Trigliserid düzeyinin düşürülmesi
- HDL düzeyinin yükseltilmesi
- Antiinflamatuar etki - CRP düzeyinde düşme
- PAI-1 düzeyinde düşme

Thiazolidinedionlar (TZD)

Böbrek Koruyucu Olası Mekanizmalar



Thiazolidinedionlar (TZD)

Böbrek Koruyucu Etki

- Albüminüriyi azaltıyor..
- Proteinüriyi azaltıyor..

DIABETES, VOL. 47, AUGUST 1998

Peroxisome Proliferator-Activated Receptor-γ Agonist, Rosiglitazone, Protects Against Nephropathy and Pancreatic Islet Abnormalities in Zucker Fatty Rats

Robin E. Buckingham, Kamal A. Al-Barazanji, C.D. Nigel Toseland, Mark Slaughter, Susan C. Connor, Andrew West, Brian Bond, Nicholas C. Turner, and John C. Clapham

Rosiglitazone (BRL 49653), a peroxisome proliferator–activated receptor-γ (PPAR-γ) agonist and potent

Thiazolidinedionlar (TZD)

Hayvan Çalışmaları

Table 1 | Animal studies reporting renal effects of TZDs

Study	TZD compound	Animal model	Duration	Effect on urine albumin or protein excretion	Effect on BP	Hemodynamic and morphological renal effects
Yoshioka *et al.*[23]	Troglitazone	Obese Zucker rats	4 and 8 weeks	↓	↓	NA
Fujii *et al.*[36]	Troglitazone	Streptozotocin-induced diabetic rats	12 weeks	↓	■	NA
Fujiwara *et al.*[37]	Troglitazone	Heminephrectomized Wistar fatty rats	24 weeks	↓	↓	NA
Isshiki *et al.*[38]	Troglitazone	Streptozotocin-induced diabetic rats	12 weeks	↓	NA	Prevention of glomerular hyperfiltration
Nicholas *et al.*[39]	Troglitazone	Streptozotocin-induced diabetic rats	3 months	↓	■	NA
Yoshida *et al.*[43]	Troglitazone	5/6 nephrectomized SHR	12 weeks	■	↓	Prevention of glomerulosclerosis
Ma *et al.*[44]	Troglitazone	5/6 nephrectomized Sprague-Dawley rats	12 weeks	↓	■	Prevention of glomerulosclerosis and glomerular cell proliferation
Yamashita *et al.*[26]	Troglitazone, pioglitazone	Streptozotocin-induced diabetic SHR	12 weeks	↓	■	Prevention of the loss of anionic sites of glomerular basement membranes
Yoshimoto *et al.*[24]	Pioglitazone	Diabetic Wistar fatty rats	13 weeks	↓	↓	Prevention of glomerulosclerosis and intrarenal arteriolosclerosis
Tanimoto *et al.*[40]	Pioglitazone	Diabetic KK/Ta mice	4 and 8 weeks	↓	■	Prevention of glomerular enlargement
Buckingham *et al.*[25]	Rosiglitazone	Obese Zucker rats	4 and 9 months	↓	↓	Prevention of glomerulosclerosis and tubulointerstitial fibrosis
Baylis *et al.*[41]	Rosiglitazone	Obese Zucker rats	6 months	↓	■	Prevention of glomerulosclerosis and tubulointerstitial fibrosis
Khan *et al.*[42]	Rosiglitazone	Obese Zucker rats	12 weeks	↓	↓	NA

BP, blood pressure; NA, not applicable; SHR, spontaneously hypertensive rats; TZD, thiazolidinedione.
↓, significant reduction of urine albumin/protein excretion or blood pressure levels, or protection against elevation of urine albumin/protein excretion or blood pressure levels observed in untreated groups; ■, no significant effect.

Thiazolidinedionlar (TZD)
İnsan Çalışmaları

Table 2 | Human studies reporting renal effects of TZDs

Study	Type of subjects	*N*	Daily doses of regimens compared	Duration	Mean effect on UAE versus baseline in TZD groups (%)	Mean effect on SBP/DBP versus baseline in TZD groups (mmHg)
Sironi *et al.*[45]	DM2, (hyp)[a]	40	200 mg Tro versus plb	8 weeks	+11%	−4/−3[b]
Imano *et al.*[33]	DM2, mA, (hyp)[a]	30	400 mg Tro versus 500 mg Met	12 weeks	−39%[c]	−3/0
Nakamura *et al.*[46]	DM2, mA or MA	32	400 mg Tro versus 5 mg Gli	12 months	−67%[c] in mA 0% in MA	−6[d]
Nakamura *et al.*[34]	DM2, mA	45	30 mg Pio versus 5 mg Gli versus 0.6 mg Vog	3 months	−66%[c]	−6/−4
Nakamura *et al.*[49]	DM2, mA	28	30 mg Pio versus plb	6 months	−59%[c]	−4[d]
Aljabri *et al.*[50]	DM2, (mA)[e], (hyp)[a]	62	30–45 mg Pio versus isophane insulin	16 weeks	−44%	−8/−5
Yanagawa *et al.*[51]	DM2, mA, (hyp)[a]	40	Pio versus Met or Gli	12 weeks	−45%[c]	NA
Hanefeld *et al.*[52]	DM2, (mA)[e], (hyp)[a]	639	15–45 mg Pio versus 850–2550 mg Met	12 months	−15%[c]	NA[f]
Schernthaner *et al.*[53]	DM2, (hyp)[a]	1199	15–45 mg Pio versus 850–2550 mg Met	12 months	−19%[c]	NA[f]
Matthews *et al.*[54]	DM2, (hyp)[a]	630	15–45 mg Pio versus 80–320 mg Gli	12 months	−10%[c]	NA[f]
Agarwal R, *et al.*[55]	DM2, MA (hyp)[a]	44	Pio versus Glip	4 months	−7%	+3.7/+2.2[b]
Lebovitz *et al.*[56]	DM2, (mA)[e], (hyp)[a]	493	4 or 8 mg Rosi versus plb	26 weeks	4 mg group: −14% 8 mg group: −22%[c]	NA
Bakris *et al.*[35]	DM2, (mA)[e], (hyp)[a]	129	8 mg Rosi versus Gli	12 months	−30%[c]	−0.1[c]/−2.3[b,c]
Sarafidis *et al.*[57]	DM2, hyp, (mA)[e]	20	4 mg Rosi	6 months	−35%[c]	−5.4[c]/−4.1[b,c]
Pistrosch *et al.*[58]	DM2, (mA)[e], (hyp)[a]	19	non-mA patients: Rosi versus Nat, mA patients: Rosi versus plb	12 weeks	non-mA patients: +18%[g], mA patients: −66%[c,g]	NA
Bakris *et al.*[59]	DM2, mA, (hyp)[a]	389	Rosi versus Gli	32 weeks	−23%[c]	−1.3[c]/−2.3[b,c]

DBP, diastolic blood pressure; DM2, subjects with type 2 diabetes mellitus; Gli, glibenclamide; Glip, glipizide; hyp, subjects with hypertension; mA, subjects with microalbuminuria; MA, subjects with macroalbuminuria, Met, metformin; NA, changes in blood pressure levels not applicable; Nat, nateglinide; plb, placebo; Pio, pioglitazone; SBP, systolic blood pressure; Tro, troglitazone; TZd, thiazolidinediones UAE, urine albumin excretion, Vog, Voglibose.

[a]A percentage of the total population was also hypertensive.

[b]Studies using ambulatory BP recordings.

[c]Significant change versus baseline levels or the other group compared.

[d]Mean change for systolic BP versus baseline in patients treated with the TZD.

[e]A percentage of the total population had microalbuminuria.

[f]Studies reporting nonsignificant decreases in BP versus baseline in both the groups compared, without giving detailed changes.

[g]Change versus the group compared.

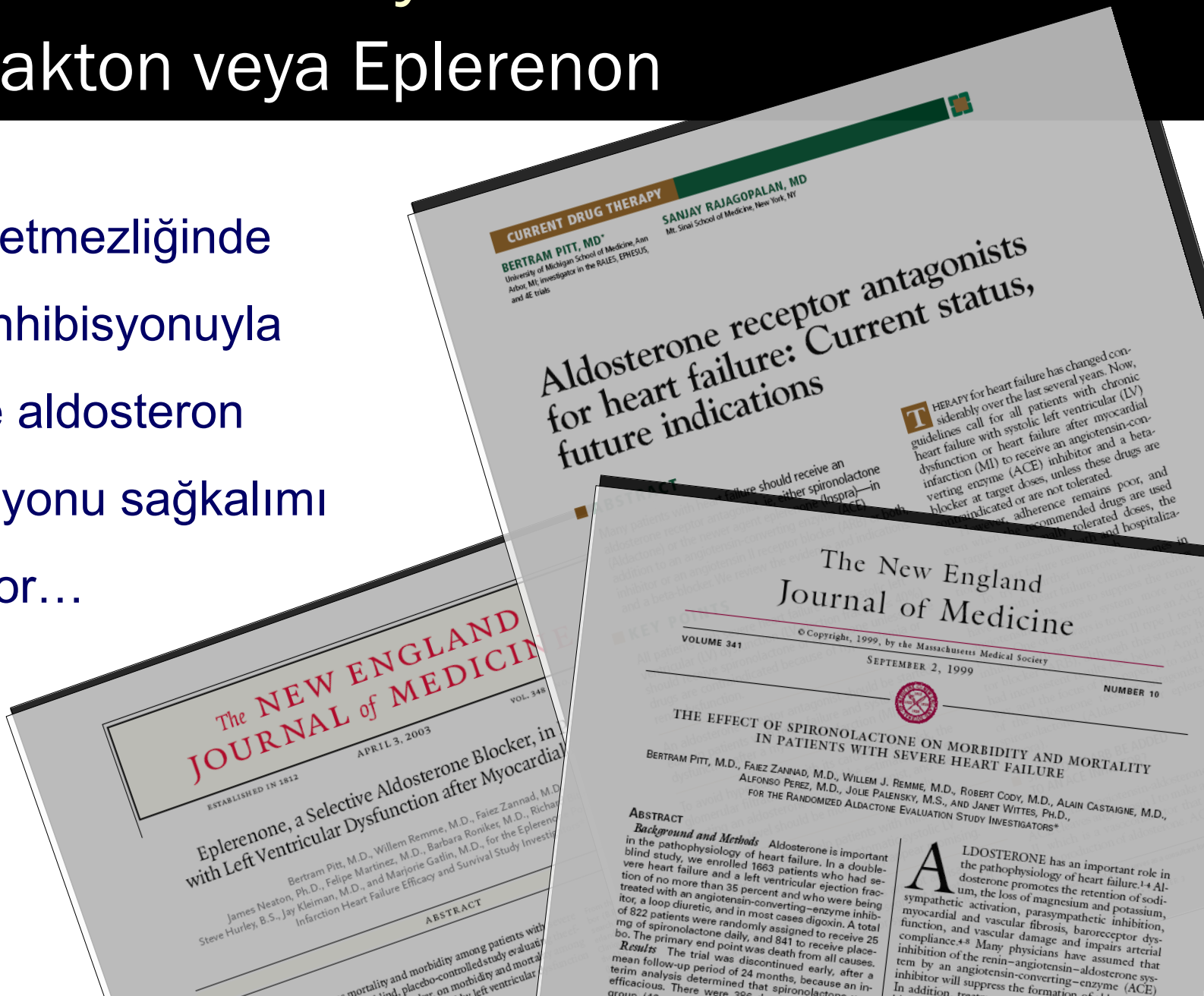
Diyabetik Nefropati Tedavisi

Aldosteron İnhibisyonu

Aldosteron İnhibisyonu

Sprinolakton veya Eplerenon

- Kalp yetmezliğinde ACE inhibisyonuyla birlikte aldosteron inhibisyonu sağkalımı uzatıyor…



Diyabetik Nefropati

Aldosteron İnhibisyonu

- Hayvan çalışmalarında aldosteronun böbrekte fibrozise yol açtığı gösterilmiştir
- Ancak klinik diyabetik nefropatide aldosteronun rolü yeterince araştırılmamıştır..

Improving Outcomes in Diabetic Nephropathy
Hipotez

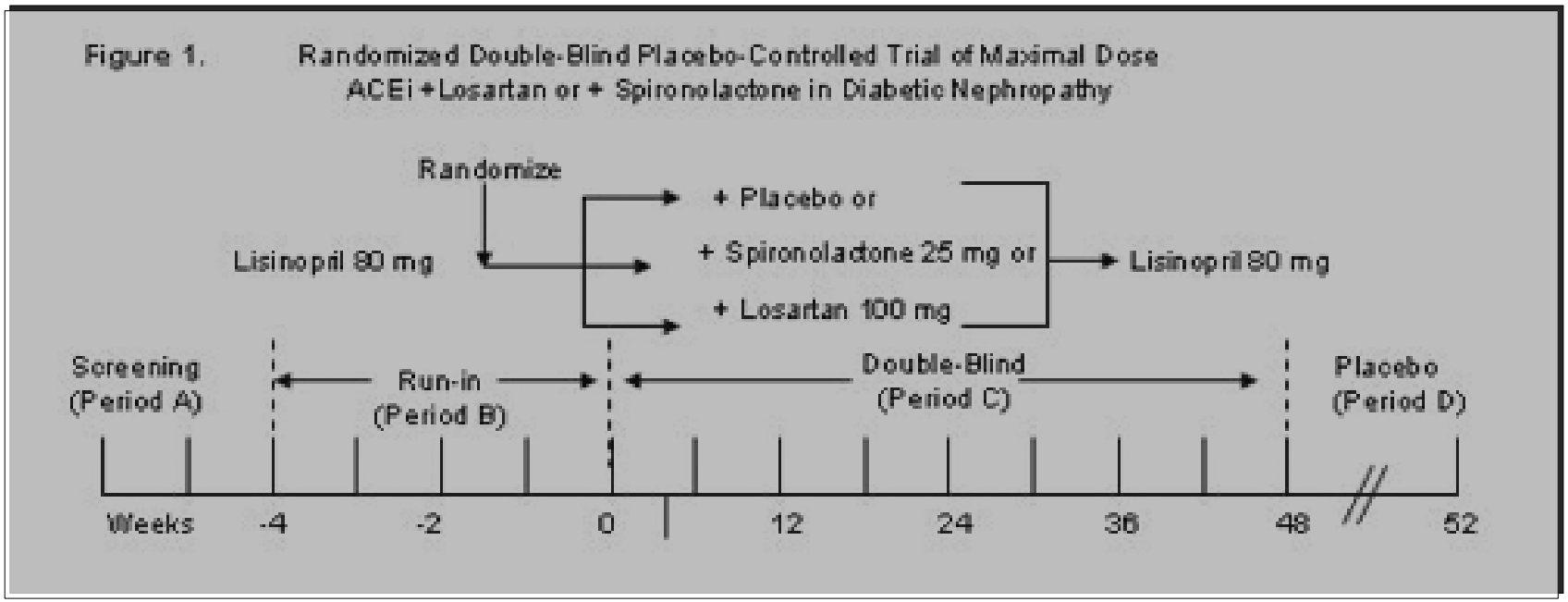
- RAA sisteminin blokajı
  - Proteinüriyi azaltır
  - Progresyonu yavaşlatır

Improving Outcomes in Diabetic Nephropathy
Tasarım

- Randomize çift-kör plasebo kontrollü
- Hastalar:
  - Farklı etnik kökenlerden
  - Tip 1 DM (n:39)
  - Tip 2 DM (n:39)
  - Sistolik KB > 130 mmHg
  - İdrar albümin / kreatinin oranı > 300
  - Lizinopril ve/veya diğer antipertansifleri kullanan…

Improving Outcomes in Diabetic Nephropathy

Tasarım



Improving Outcomes in Diabetic Nephropathy
Sonlanım Noktaları

- Öncelikli ölçüt:
  - İdrar albümin / kreatinin oranındaki değişim (mikroalbüminüride değişim)
- İkincil ölçütler:
  - İdrar TGF β miktarında değişim
  - Plazma renin, angiotensin II, aldosteron düzeylerinde değişim
- Güvenlik ölçütleri:
  - Ambulatuar KB izlemi
  - Serum potasyum ve kreatinin düzeyi

Diyabetik Nefropati Tedavisi

Renin İnhibisyonu

Aliskiren

Diyabetik Ratlarda Albüminüriyi Azaltıyor..

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Effects of Aliskiren on Blood Pressure, Albuminuria, and (Pro)Renin Receptor Expression in Diabetic TG (mREN-2)27 Rats

David L. Feldman*; Liang Jin; Hong Xuan; Aurelie Contrepas; Yinong Zhou; Randy L. Webb; Dominik N. Mueller; Sandra Feldt; Frederick Cumin; Wieslawa Maniara; Elke Persohn; Helmut Schuetz; A. H. Jan Danser; and Genevieve Nguyen

From Novartis Institutes for Biomedical Research (D.L.F., L.J., H.X., Y.Z., R.L.W., F.C., W.M.), E. Hanover, NJ and Cambridge, Mass; Inserm Unit 833 (A.C., G.N.), Paris, France; Chaire de Médecine Expérimentale (A.C., G.N.), Collège de France, Paris; Max-Delbruck-Center (D.N.M., S.F.), Berlin-Buch, Germany; Novartis Pharma AG (E.P., H.S.), Basel, Switzerland; and the Department of Pharmacology (A.H.J.D.), Erasmus MC, Rotterdam, The Netherlands.

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Abstract—The aim of this study was to explore the effects of the renin inhibitor aliskiren in streptozotocin-diabetic TG(mRen-2)27 rats. Furthermore, we investigated in vitro the effect of aliskiren on the interactions between renin and the (pro)renin receptor and between aliskiren and prorenin. Aliskiren distributed extensively to the kidneys of normotensive (non)diabetic rats, localizing in the glomeruli and vessel walls after two hours exposure. In diabetic TG(mRen-2)27 rats, aliskiren (10 or 30 mg/kg/d, 10 weeks) lowered blood pressure, prevented albuminuria, and suppressed renal transforming growth factor (TGF)-beta and collagen I expression versus vehicle. Aliskiren reduced (pro)renin receptor expression in glomeruli, tubules, and cortical vessels compared to vehicle (in situ hybridization). In human mesangial cells, aliskiren (0.1 μmol/L to 10 μmol/L) did not inhibit binding of ^{125}I-renin to the (pro)renin receptor, nor did it alter the activation of extracellular signal-regulated kinase (ERK) 1/2 by renin (20 nmol/L) preincubated with aliskiren (100 nmol/L) or affect gene expression of the (pro)renin receptor. Evidence was obtained that aliskiren binds to the active site of prorenin. The above results demonstrate the antihypertensive and renoprotective effects of aliskiren in experimental diabetic nephropathy. The evidence that aliskiren can reduce in vivo gene expression for the (pro)renin receptor and that it may block prorenin-induced angiotensin generation supports the need for additional work to reveal the mechanism of the observed renoprotection by this renin inhibitor.

Aliskiren

Tip 2 Diyabetik Nefropatide Proteinüriyi Azaltıyor..

- 15 hastalık prospektif araştırma
- Hastalar Tip 2 diyabetik ve albüminürik

http://www.kidney-international.org original article

Time course of the antiproteinuric and antihypertensive effects of direct renin inhibition in type 2 diabetes

F Persson[1], P Rossing[1], KJ Schjoedt[1], T Juhl[1], L Tarnow[1], CDA Stehouwer[2], C Schalkwijk[2], F Boomsma[3], E Frandsen[4] and H-H Parving[5,6]

Aliskiren

Tip 2 Diyabetik Nefropatide Proteinüriyi Azaltıyor..

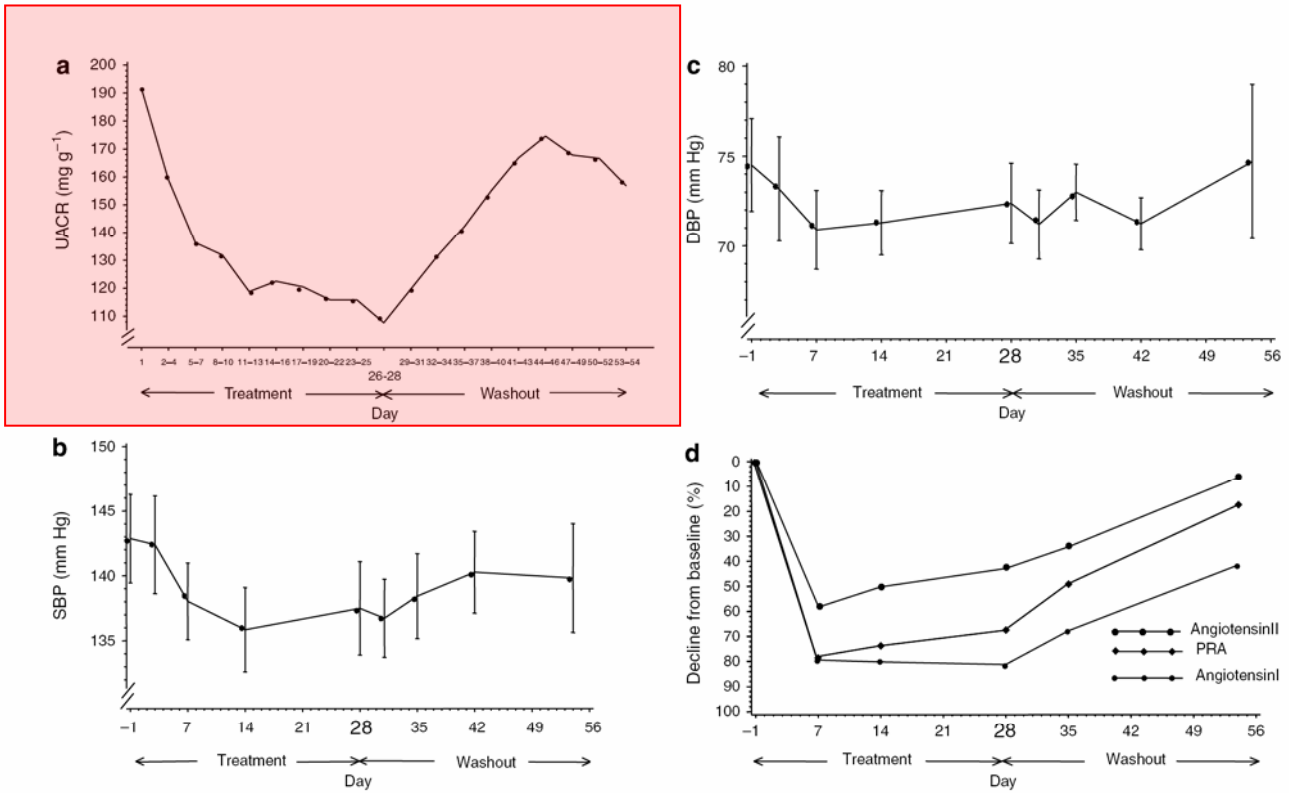

Figure 2 | Effect of renin inhibition on UACR, 24 h BP and RAAS components. (**a**) UACR (mg g^{-1}) (geometric means) in 15 type 2 diabetic patients with micro- or macroalbuminuria treated with aliskiren for 28 days followed by 28 days washout. (**b**) 24 h SBP (s.e.m) in 15 type 2 diabetic patients with micro- or macroalbuminuria treated with aliskiren for 28 days followed by 28 days washout. (**c**) 24 h DBP (s.e.m) in 15 type 2 diabetic patients with micro- or macroalbuminuria treated with aliskiren for 28 days followed by 28 days washout. (**d**) Plasma renin activity, Ang I and Ang II (ratio of geometric means relative to baseline) in 15 type 2 diabetic patients with micro- or macroalbuminuria treated with aliskiren for 28 days followed by 28 days washout.

Diyabetik Nefropati Tedavisi

Vitamin D

Diyabetik Nefropati Gelişimi
Vitamin D'nin Rolü

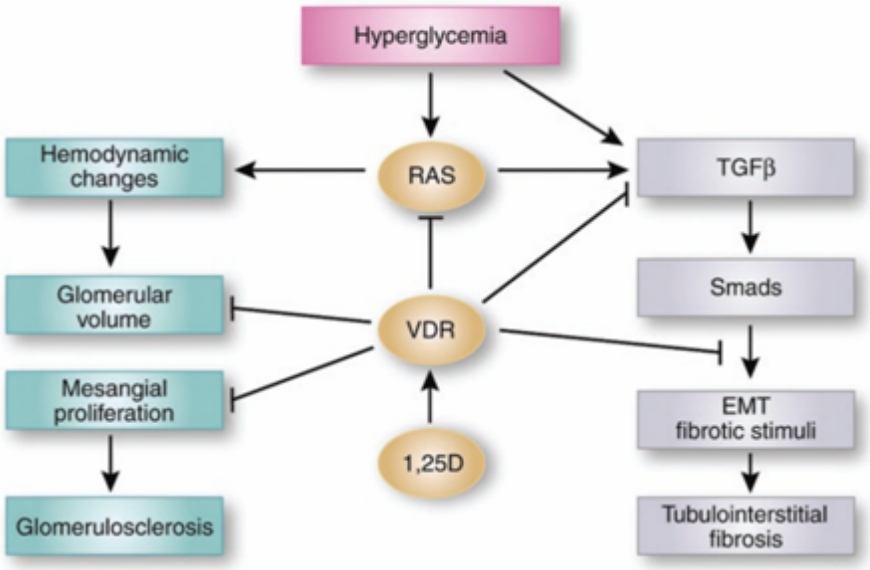

Figure 1 | Proposed effects of active vitamin D metabolites on development of diabetic nephropathy. Hyperglycemia stimulates the intrarenal renin–angiotensin system (RAS) and formation of transforming growth factor-β (TGF-β) and other cytokines as well as proteinuria. TGF-β induces tubular epithelial-to-mesenchymal transition and stimulation of profibrotic signals. Increased activity of the RAS induces hemodynamic changes in the glomerulus followed by increased glomerular volume, mesangial proliferation, and podocyte injury. Active vitamin D metabolites bind to the vitamin D receptor (VDR) and inhibit stimulation of the RAS as well as podocyte and mesangial-cell proliferation. In addition, active vitamin D counterbalances fibrogenesis by inhibiting TGF-β indirectly via the activation of hepatocyte growth factor. In consequence, active vitamin D metabolites reduce glomerulosclerosis and tubulointerstitial fibrosis.

Vitamin D Eksikliği = Diyabetik Nefropatiye Eğilim

Diyabetik 'VDR Knock Out' Fareler Üzerinde Araştırma

http://www.kidney-international.org original article

see commentary on page 141

Renoprotective role of the vitamin D receptor in diabetic nephropathy

Z Zhang[1,3], L Sun[1,3], Y Wang[1,3], G Ning[2], AW Minto[1], J Kong[1], RJ Quigg[1] and YC Li[1]

[1]Division of Biological Sciences, Department of Medicine, The University of Chicago, Chicago, Illinois, USA and [2]The Huck Institutes for Life Sciences, The Pennsylvania State University, University Park, Pennsylvania, USA

1,25-Dihydroxyvitamin D3 negatively regulates the renin–angiotensin system (RAS), which plays a critical role in the development of diabetic nephropathy. We tested if mice lacking the vitamin D receptor (VDR) are more susceptible to hyperglycemia-induced renal injury. Diabetic VDR knockout mice developed more severe albuminuria and glomerulosclerosis due to increased glomerular basement membrane thickening and podocyte effacement. More fibronectin (FN) and less nephrin were expressed in the VDR knockout mice compared to diabetic wild-type mice. In receptor knockout mice, increased renin, angiotensinogen, transforming growth factor-β (TGF-β), and connective tissue growth factor accompanied the more severe renal injury. 1,25-Dihydroxyvitmain D3 inhibited high glucose (HG)-induced FN production in cultured mesangial cells and increased nephrin expression in cultured podocytes. 1,25-Dihydroxyvitmain D3 also suppressed HG-induced activation

In both type I and type II diabetic mellitus, diabetic nephropathy is the most common renal complication that often leads to end-stage kidney disease with its attendant renal failure and high mortality.[1] Diabetic nephropathy is a long-term complication, characterized initially by glomerular and tubuloepithelial hypertrophy, and thickening of glomerular and tubular basement membranes, followed by hyperfiltration, albuminuria, glomerulosclerosis, and tubulointerstitial fibrosis, leading eventually to end-stage kidney disease.[2] The pathogenesis of diabetic nephropathy is complex and involves direct actions of extracellular glucose on glomerular, tubular, vascular, and interstitial cells. These actions lead to the stimulation of cytokines and growth factors, such as angiotensin II (Ang II), transforming growth factor-β (TGF-β), and monocyte chemoattractant protein (MCP)-1, which play a major role in the development of diabetic nephropathy.[3–5]

Diyabetik Nefropati Tedavisi

DİĞER

Diyabetik Nefropati – Gelecek Tedaviler

Relaxin

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Relaxin Ameliorates Fibrosis in Experimental Diabetic Cardiomyopathy

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Fibrosis (extracellular matrix (ECM) accumulation) is the final end-point in diabetic cardiomyopathy. The current study evaluated the therapeutic effects of the anti-fibrotic hormone relaxin in streptozotocin (STZ)-treated transgenic mRen-2 rats, which undergo pathological and functional features similar to human diabetes. Twelve-week old hyperglycaemic mRen-2 rats, normoglycaemic control rats, and animals treated with recombinant human gene-2 (H2) relaxin (H2-RLX) from weeks ten-twelve were assessed for various measures of left ventricular (LV) fibrosis, hemodynamics and function, while the mechanism of relaxin's actions was also determined. Hyperglycaemic mRen-2 rats had increased LV collagen concentration (fibrosis) and gelatinase activity (all $p<0.05$ vs controls), but equivalent levels of interstitial collagenase and TIMP-1 to that measured in control rats. The increased LV fibrosis associated with diabetic animals led to significant alterations in the E/A wave ratio and E-wave deceleration time (both $p<0.05$ vs controls) in the absence of blood pressure changes, reflective of myocardial stiffness and LV diastolic dysfunction. H2-RLX treatment of diabetic rats led to significant decreases in interstitial and total LV collagen deposition (both $p<0.05$ vs diabetic group), resulting in decreased myocardial stiffness and improved LV diastolic function, without affecting non-diabetic animals. The protective effects of H2-RLX in diabetic rats were associated with a reduction in mesenchymal cell differentiation and TIMP-1 expression in addition to a promotion of ECM-degrading MMP-13 (all $p<0.05$ vs diabetic group), but were independent of blood pressure regulation. These findings demonstrate that relaxin is an anti-fibrotic with rapid-occurring efficacy, and may represent a novel therapy for the treatment of diabetes.

Key words: diabetic cardiomyopathy • fibrosis • matrix metalloproteinases • relaxin • TIMP-1

Diyabetik Nefropati Tedavisi

Ruboxistaurin Böbreği Korumuyor mu?

Diyabetik Retinopati Çalışmaları

The Effect of Ruboxistaurin on Visual Loss in Patients With Moderately Severe to Very Severe Nonproliferative Diabetic Retinopathy

Initial Results of the Protein Kinase C β Inhibitor Diabetic Retinopathy Study (PKC-DRS) Multicenter Randomized Clinical Trial

The PKC-DRS Study Group*

DIABETES, VOL. 54, JULY 2005

Ruboxistaurin nefropatiye gidişi durdurmuyor !?

Ruboxistaurin

RUBOXISTAURIN TREATMENT OF NPDR AND VISUAL LOSS

TABLE 3
Adverse events from PKC-DRS and PKC-DMES with incidence of at least 1% and statistically significant difference among treatment groups

Events*	Placebo	RBX 4/8 mg/day	RBX 16 mg/day	RBX 32 mg/day	*P* value
n	237	228	238	235	
Coronary artery disease NOS	16 (6.8)	8 (3.5)	31 (13.0)	11 (4.7)	<0.001
Diarrhea NOS	40 (16.9)	31 (13.6)	58 (24.4)	35 (14.9)	0.010
Flatulence	4 (1.7)	3 (1.3)	10 (4.2)	1 (0.4)	0.020
Atrioventricular block first degree	0	3 (1.3)	3 (1.3)	8 (3.4)	0.023
Asthma NOS	2 (0.8)	4 (1.8)	4 (1.7)	11 (4.7)	0.028
Nephropathy NOS	1 (0.4)	2 (0.9)	7 (2.9)	1 (0.4)	0.031
Proteinuria	2 (0.8)	3 (1.3)	9 (3.8)	2 (0.9)	0.038
Hyperkeratosis	13 (5.5)	15 (6.6)	6 (2.5)	5 (2.1)	0.038
Dysuria	3 (1.3)	2 (0.9)	4 (1.7)	10 (4.3)	0.041

Data are *n* (%). *Preferred term from MedDRA version 4.0. NOS, not otherwise specified.

- Ruboxistaurin böbrekleri korumuyor mu?

Kidney Outcomes in Long-Term Studies of Ruboxistaurin for Diabetic Eye Disease

Katherine R. Tuttle,* Janet B. McGill,† Douglas J. Haney,‡ Toni E. Lin,‡ Pamela W. Anderson;‡ for the PKC-DRS, PKC-DMES, and PKC-DRS 2 Study Groups

Providence Medical Research Center and University of Washington School of Medicine, Spokane, Washington; †Department of Medicine, Washington University, St. Louis, Missouri; and ‡Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

Background: A pilot study showed that ruboxistaurin (RBX), a protein kinase C β inhibitor, significantly decreased albuminuria and stabilized kidney function over 1 yr in patients who had diabetic nephropathy and persistent macroalbuminuria despite receiving the current standard of care, including renin-angiotensin system inhibition. In contrast, in a trial of patients with diabetic retinopathy, investigators reported the adverse event "diabetic nephropathy" more frequently in patients who received RBX.

Design, setting, participants, and measurements: The purpose of this study was to evaluate long-term effects of RBX on kidney outcomes among patients with diabetic eye disease in three diabetic retinopathy trials (n = 1157). Baseline-to-study end changes in estimated GFR (eGFR) were calculated. Kidney outcomes included doubling of serum creatinine, development of advanced chronic kidney disease (stages 4 to 5), and death.

Results: Baseline eGFR was 81.6 ± 26.0 ml/min per 1.73 m^2. In the combined placebo and RBX treatment groups, eGFR decreased by 11.0 ± 19.6 ml/min per 1.73 m^2 during median follow-up of 33 to 39 mo. At least one kidney outcome occurred in 11.3% of patients. Frequency of doubling of serum creatinine was 6.0%, progression to advanced chronic kidney disease was 4.1%, and death was 4.1%. Kidney outcome rates did not differ by treatment assignment.

Conclusions: Long-term kidney outcomes in patients with diabetic eye disease were similar in placebo and RBX groups. In conclusion, large-scale, prospective trials in patients with diabetic nephropathy are needed to confirm safety and potential benefits of RBX on clinical outcomes.

Clin J Am Soc Nephrol 2: 631-636, 2007. doi: 10.2215/CJN.00840207

Kidney Outcomes in Long-Term Studies of Ruboxistaurin for Diabetic Eye Disease

Katherine R. Tuttle,* Janet B. McGill,† Douglas J. Haney,‡ Toni E. Lin,‡
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**Providence Medical Research Center and University of Washington School of Medicine, Spokane, Washington; †Department of Medicine, Washington University, St. Louis, Missouri; and ‡Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana*

Table 1. Baseline characteristics by assignment to placebo or RBX in long-term studies of diabetic eye disease[a]

Characteristic	Placebo	RBX 32 mg/d	Total	*P*
n	577	580		
Age (yr)	57.8 ± 11.0	57.7 ± 11.3	57.8 ± 11.2	0.87
Male (*n* [%])	373 (65)	362 (63)	735 (64)	0.43
Type 2 diabetes (*n* [%])	491 (85)	499 (86)	990 (86)	0.65
Duration of diabetes (yr)	16 ± 8	16 ± 8	16 ± 8	0.58
HbA_{1c} (%)	8.4 ± 1.4	8.5 ± 1.5	8.4 ± 1.5	0.38
Non-smokers (*n* [%])	525 (91)	526 (91)	1051 (91)	0.86
BMI (kg/m^2)	32.2 ± 6.7	32.1 ± 7.4	32.1 ± 7.1	0.91
ACEI (*n* [%])	286 (50)	288 (50)	574 (50)	0.98
ARB (*n* [%])	69 (12)	70 (12)	139 (12)	0.97
ACEI and ARB (*n* [%])	11 (2)	12 (2)	23 (2)	0.84
Systolic BP (mmHg)	139 ± 18	137 ± 18	138 ± 18	0.05
Diastolic BP (mmHg)	78 ± 10	78 ± 10	78 ± 10	0.93

[a]ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; HbA_{1c}, glycosylated hemoglobin, RBX, ruboxistaurin.

Kidney Outcomes in Long-Term Studies of Ruboxistaurin for Diabetic Eye Disease

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Providence Medical Research Center and University of Washington School of Medicine, Spokane, Washington; †Department of Medicine, Washington University, St. Louis, Missouri; and ‡Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

Table 2. Kidney function by assignment to placebo or RBX in long-term studies of diabetic eye disease[a]

Measurement	Placebo		RBX 32 mg/d		Total		*P*
	N	Mean ± SD	*N*	Mean ± SD	*N*	Mean ± SD	
Baseline							
eGFR (ml/min per 1.73 m^2)	576	82.4 ± 26.0	579	80.8 ± 26.0	1155	81.6 ± 26.0	0.30
calculated creatinine clearance (ml/min)	570	115.6 ± 46.4	575	113.0 ± 46.8	1145	114.3 ± 46.6	0.35
serum creatinine (mg/dl)	576	1.0 ± 0.3	579	1.0 ± 0.4	1155	1.0 ± 0.3	0.22
Study end (after 33 to 39 mo of treatment)							
eGFR (ml/min per 1.73 m^2)	561	71.1 ± 26.8	557	70.4 ± 26.3	1118	70.8 ± 26.5	0.67
calculated creatinine clearance (ml/min)	555	101.4 ± 44.2	553	100.1 ± 45.0	1108	100.7 ± 44.6	0.63
serum creatinine (mg/dl)	561	1.2 ± 0.7	557	1.2 ± 0.8	1118	1.2 ± 0.7	0.56
Change (after 33 to 39 mo of treatment)							
eGFR (ml/min per 1.73 m^2)	560	−11.3 ± 19.4	556	−10.7 ± 19.8	1116	−11.0 ± 19.6	0.61
calculated creatinine clearance (ml/min)	555	−14.2 ± 26.0	552	−13.6 ± 27.3	1107	−13.9 ± 26.6	0.69
serum creatinine (mg/dl)	560	0.2 ± 0.5	556	0.2 ± 0.6	1116	0.2 ± 0.6	0.90

[a]eGFR, estimated GFR; MDRD, Modification of Diet in Renal Disease. eGFR estimated by the MDRD formula. Creatinine clearance calculated by the Cockroft-Gault formula.

Kidney Outcomes in Long-Term Studies of Ruboxistaurin for Diabetic Eye Disease

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- Ruboxistaurin nefropatinin progresyonu üzerinde etkisiz bulunmuş!

Table 3. Kidney outcomes by assignment to placebo or RBX long-term studies of diabetic eye disease[a]

Characteristic	Placebo	RBX 32 mg/d	Total	*P*
Doubling of serum creatinine	6.1% (35/577)	5.9% (34/580)	6.0% (69/1157)	0.88
Progression to advanced CKD	4.3% (25/577)	3.8% (22/580)	4.1% (47/1157)	0.64
Death	4.7% (27/577)	3.6% (21/580)	4.1% (48/1157)	0.37
At least one kidney outcome	11.8% (68/577)	10.9% (63/580)	11.3% (131/1157)	0.62

[a]CKD, chronic kidney disease.