Mini-Lecture 4

혈액투석 환자에서의 혈당관리

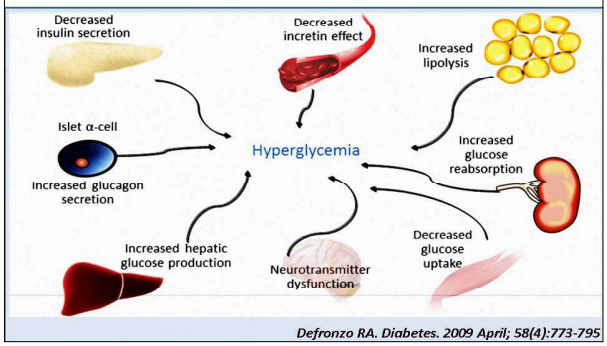
관동의대 신장내과

문 성 진

목차

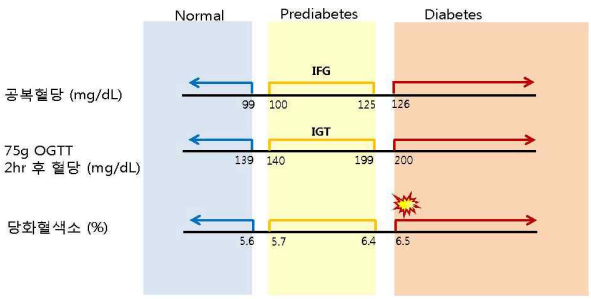
- ✓ 일반인에서 당뇨의 기전, 진단기준,
- ✓ 치료목표 (HbA1C 가 낮을 수록 좋은가?)
- ✓ 당뇨 혈액투석 환자의 특징
  - ✓HbA1C 의 정확성
  - ✓Burnt-out diabetes
- ✓ 혈당 조절 약제
  - ✓인슐린
  - ✓경구혈당강하제

Pathophysiology of DM



Defronzo RA. Diabetes. 2009 April; 58(4):773-795

정상, 당뇨전단계, 당뇨병



The goal for glycemic control

- Diabetes Diabetes Control and Complications Trial / Epidemiology of Diabetes (DCCT/EDIC) - 1993년
- UK Prospective Diabetes Study (UKPDS) -1998년
- Kumamoto studies -1995년

- STENO-2 study; the effects of intensive multifactorial therapy
- ADVANCE

- **Strict glycemic control**
  - **Reduction in microvascular events,**
  - **Inconsistent results of macrovascular events**

UKPDS

: 고혈당 & 미세혈관 합병증

Table 29.2 Trials comparing intensive with standard (conventional) glycemic control in type 2 diabetes.

Trial	Number	Duration of follow-up	Age	Duration of diabetes	Baseline HbA_{1c}%	Intensive HbA_{1c}%		Conventional HbA_{1c}%	Relative risk reduction: Microvascular %	Microvascular P	Macrovascular %	Macrovascular P
UKPDS	3867[a]	10	53	New	7.1[b]	7.0	vs	7.9	↓ 25%	0.009	↓ 16%[c]	0.052[d]
UKPDS (post-trial follow-up)	2998	8.5	63	10	–		–		↓ 24%	0.001	↓ 15%[c]	0.014
ADVANCE	11,140	5	66	8	7.5	6.5	vs	7.3	↓ 14%	0.01	↓ 6%	0.32[e]
ACCORD[a]	10,251	3.5[a]	62	10	8.3	6.4[a]	vs	7.5	↓ 33%	0.005[f]	↓ 10%	0.16[b]
VADT	1791	5.6	60	11.5	9.4	6.9	vs	8.4	↓ 2.5[g]	0.05	↓ 12%	0.14[b]

- UKPDS 에서 미세혈관 합병증은 유의하게 감소
- UKPDS 에서 대혈관 합병증은 감소경향은 있으나 통계적 유의성은 없었음

The Lower The Better?

ADVANCE/ACCORD/VADT

: 고혈당 & 대혈관 합병증

- UKPDS
  : 당뇨 초기 환자, 점진적 혈당 조절
- ADVANCE/ACCORD/VADT
  : 오래된 당뇨 환자, 급격한 혈당 조절

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사망률 증가로 조기 종료

- ADVANCD/ACCORD/VADT 에서 대혈관 합병증은 경향은 보였으나 통계적 유의성 없었음
- ACCORD 에서는 사망률이 더 증가함

The goal for glycemic, blood pressure, & lipid

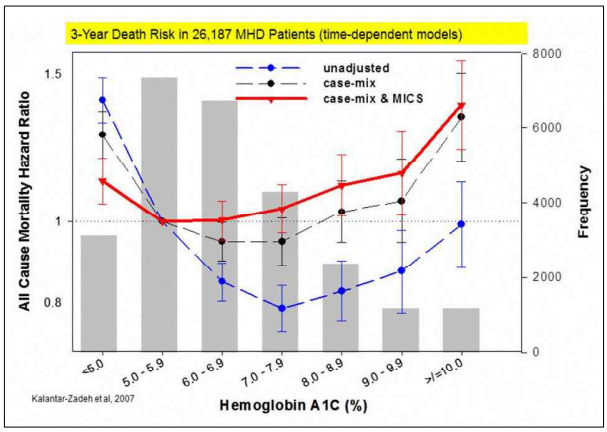
Table 9—*Summary of glycemic recommendations for many nonpregnant adults with diabetes*

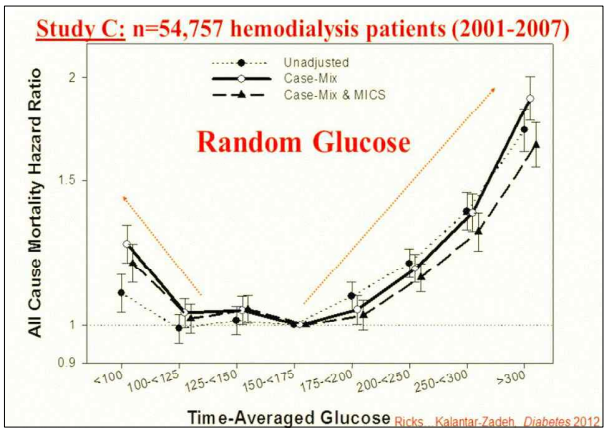
A1C	<7.0%*
Preprandial capillary plasma glucose	70–130 mg/dL* (3.9–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (<10.0 mmol/L)

- *Goals should be individualized based on:
  - duration of diabetes
  - age/life expectancy
  - comorbid conditions
  - known CVD or advanced microvascular complications
  - hypoglycemia unawareness
  - individual patient considerations
- More or less stringent glycemic goals may be appropriate for individual patients
- Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals

†Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Diabetes Care. 2013 Jan;36 Suppl 1:S11-66





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Individualization of glycemic goal !!!

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Diabetes Care. 2013 Jan;36 Suppl 1:S11-66

Two issues in diabetic dialysis patients

- What measure of glycemic control is the most reliable?
- "Burnt-out diabetes",
  - Normoglycemia or even frequent hypoglycemic episodes

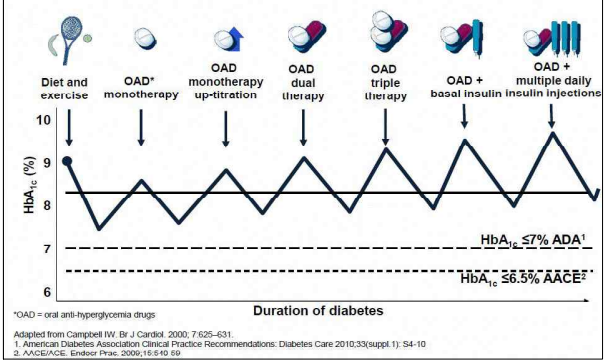
Glucose monitoring: HbA1c

- **투석 환자에서 A1c 측정의 부정확도**
  - 측정 방법의 간섭 현상은 최근 대부분의 병원에서 사용하는 affinity chromatography에서는 발생하지 않음
- **False decrement of A1c**
  - Reduced RBC life span
  - Recent transfusion
  - Accelerated erythropoiesis due to administration of EPO (a modest fall of 0.5-0.7% in HbA1c along with the rise in total hemoglobin)
- **False elevation of A1c**
  - Uremia induced carbamylation
  - Metabolic acidosis in dialysis patients

Table 1. Diagnostic Tests to Assess Integrated Glucose Control in Patients With Diabetes Mellitus

Diagnostic Test	Glycemic Control Period	Conditions Affecting Interpretation	Advantages	Disadvantages
Hemoglobin A_{1c}	2-3 mo	Hemoglobinopathies, diseases of shortened erythrocyte life span	Used in major trials that determined thresholds of glycemic control. Routine testing available in most clinical laboratories	No information about short-term glucose control
Fructosamine	2-3 wk	Proteinuria, dysproteinemias, malnutrition, thyroid abnormalities, liver disease, pregnancy, steroid therapy	Unaffected by disease states affecting hemoglobin	Reference levels lacking Testing not offered routinely by most clinical laboratories
Glycated albumin	2 wk	Proteinuria, dysproteinemias, malnutrition, thyroid abnormalities, liver disease, pregnancy, steroid therapy	Unaffected by disease states affecting hemoglobin	Reference levels lacking Testing not offered routinely by most clinical laboratories

Conservative management of glycemia: Traditional stepwise approach



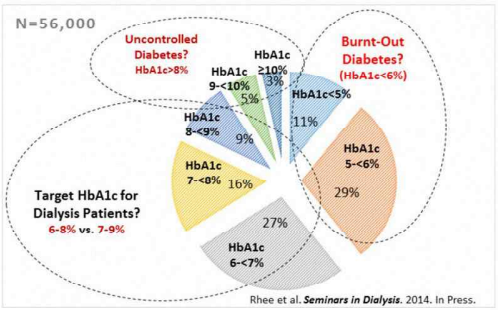
Adapted from Campbell IW. Br J Cardiol. 2000; 7:625–631.
1. American Diabetes Association Clinical Practice Recommendations: Diabetes Care 2010;33(suppl.1): S4-10
2. AACE/ACE. Endocr Prac. 2006;16:640-59

The concept of Burnt-Out Diabetes

- Many patients with diabetic nephropathy → ESRD
- CKD progression → require less & less & less insulin injection → → stop insulin (to avoid hypoglycemia)
- → some will have to stop all oral hypoglycemic agents
- → A1c <6% in 30% of diabetic dialysis patients!!
- *Does ESRD burn out diabetes mellitus e.g. through Wasting & Malnutrition?*

Kalantar-Zadeh et al, *JREN* 2009
Kovesdy et al, *Seminar Dial* 2010

One-third of diabetic dialysis patients have "Burnt-Out" Diabetes



Causes of Burnt-Out Diabetes in CKD

Decreased renal clearance of insulin
Decreased hepatic clearance of insulin
Impaired renal insulin degradation
Increased insulin half-life
Decline in renal gluconeogenesis
Deficient catecholamine release
Other impacts of uremia on glucose homeostasis
Diminished food intake due to anorexia, diabetic gastroparesis, etc.
Protein-energy wasting (malnutrition-inflammation complex)
Loss of body weight and fat mass
Comorbiod conditions
Hypoglycemia during hemodialysis treatments
Effects of peritoneal dialysis on glucose metabolism
Prescribed medications
Imposed dietary restrictions
Apparently low A1c due to confounding by uremia or anemia

Kovesdy et al, Semin Dial 2010; 23(2):148-56

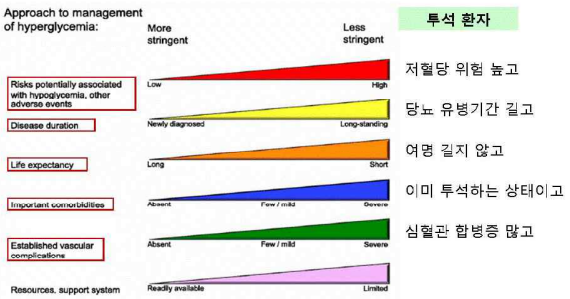
Glycemic Control Target ?
: Patient Centered Target!!!

Which drug do I prescribe ?
: Patient Centered drugs!!!

- **A**: Age
- **B**: Body weight
- **C**: Complication
- **D**: Diabetes Duration
- **E**: etiology, education, economy

Points to be considered in dialysis patients

혈당 조절 목표를 less stringent하게 해야 한다.



Goal of glycemic control in dialysis patient

- Target of HbA1c in dialysis patients
  - without comorbidity
    : ~7.0%
  - with comorbidity or recurrent hypoglycemia
    : above 7.0%
    : 7.5% or 8.0% can be acceptable in specific condition
- Target of fasting & post-prandial 2 hour glucose level
  - Fasting : 70-130 mg/dL
  - PP2: <180

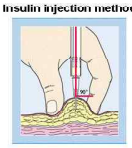
혈당 조절 약제

- 인슐린 vs 경구 약제
- 일단 투석을 시작하면 인슐린을 선호
- 그러나 투석 전부터 경구 약제로 잘 조절되던 환자를 굳이 인슐린으로 바꿀 필요는 없음
- 인슐린이든, 경구 약제든 투석 환자는 용량 조절에 매우 유의해야 함

Insulin injection

Best and Banting

Insulin injection method



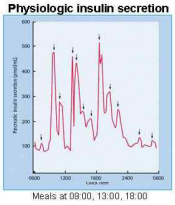
- 수직
- 피하 지방 (근육이 아님)
- 주사 위치를 지속적 변경

Insulin therapy milestones

1922	Isolation of insulin and treatment of the first patient
1936	Protamine insulin
1946	NPH isophane insulin
1951	Zinc lente insulin
1959	Biphasic insulin
1972	Continuous subcutaneous insulin infusion
1980	rDNA human insulin in humans
1981	Insulin pens
1987	Monomeric short-acting insulins
1987	Soluble prolonged-action insulin
1996	Rapid-acting insulin analog
2001	Long-acting insulin analogs

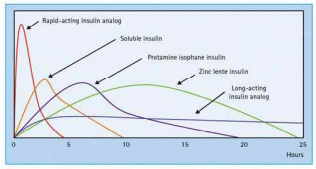
Physiology of insulin injection

Physiologic insulin secretion

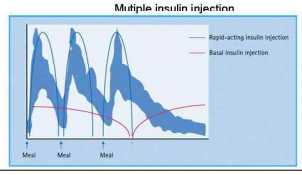


Meals at 09.00, 13:00, 18:00

Insulins



Multiple insulin injection



Insulin preparations

: acting duration

- **Rapid acting insulin** (acting time: 15min ~ 2hr)
  - apidra, humalog, novorapid
  - N/S or DW 에 mix 해서 iv infusion 가능함
  - 식후 혈당 조절
  - iv insulin, insulin pump 에 사용
- **Short acting insulin** (acting time: 2 ~ 6hr)
  - regular insulin (RI)
- **Intermediate acting insulin** (acting time: 8 ~ 16hr)
  - NPH
- **Long acting insulin** (acting time: ~ 24hr)
  - lantus, levemir
  - iv infusion 불가 !
  - 저혈당이 적다

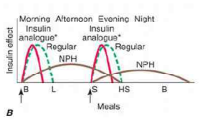
Insulin preparations

: biphasic insulins

- Humalog mix 25/75
  - rapid : intermediate = 25%: 75%
- Humalog mix 50/50
  - rapid : intermediate = 50%: 50%
- Novomix 70/30
  - rapid : intermediate = 70%: 30%
- Novomix 50/50
  - rapid : intermediate = 50%: 50%

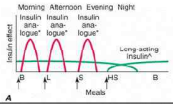
Method of insulin injection (1)

- **Basal insulin**
  - lantus or levemir (24hr 지속형)
  - Once daily injection
  - Less hypoglycemia
- **Basal Insulin + OHA bid**
  - basal insulin (취침전) + 디아미크롱 (아침/저녁 식전)



Method of insulin injection (2)

- **Premix insulin bid (아침/저녁 식전)**
  - 인슐린 용량; 아침:저녁 = 2:1
- **Premix insulin tid (아침/점심/저녁 식전)**
  - 인슐린 용량; 아침:점심:저녁 = 1:1:1
- **Basal + Bolus**
  - basal insulin (취침전) + rapid acting insulin (아침/점심/저녁 식전)



Insulin dose titration

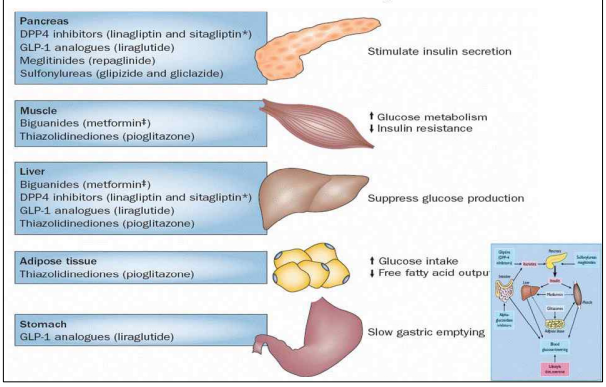
- **Renal & hepatic metabolism of insulin**
  - Decreased in dialysis patients
  - Balance between altered insulin resistance & clearance as renal dysfunction progresses is difficult to predict
  - so insulin adjustment is often largely empiric

- **Initial dose of insulin without CKD**
  - 10 units or 0.2 units/kg
- **Initial dose of insulin with eGFR 10 ~ 50 mL/min**
  - 7 units (75% of 10 units)
- **Initial dose of insulin with eGFR <10 mL/min**
  - 5 ~ 7 units (50% of 10 units)

Key points in insulin therapy in dialysis patients

- 혈당 조절 목표치를 환자에 따라서 다르게 잡고, 저혈당이 발생하면 서까지 혈당 조절을 철저하게 할 필요는 없음
  - ~7.0, ~7.5%, ~8.0%
- 투석 전후로 인슐린 요구량이 달라질 수 있음
  - 환자마다 투석에 따른 fluctuation 관찰 후 인슐린 요구량 및 투여 시간 (투석 전 후) 결정
- 투석 환자에서 권장되는 인슐린이 따로 있지는 않음
- 저혈당과 고혈당이 반복되는 환자는 식사 때마다 인슐린 사용을 권장하는 것이 좋음
  1) basal qd + bolus tid
  2) 50:50 premix insulin tid

Anti-diabetic drugs



Oral hypoglycemic agents: SU

First-generation sulfonylureas	
Acetohexamide**	Avoid use
Chlorpropamide	GFR 50-80 mL/min/1.73 m²: reduce dose 50%, GFR <50 mL/min/1.73 m²: avoid use
Tolazamide	Avoid use
Tolbutamide	Avoid use
Second-generation sulfonylureas	
Glipizide	No dose adjustment
Glimepiride	Start conservatively at 1 mg daily
Glyburide	Avoid use
Gliclazide**	No dose adjustment

- **Glipizide**: 다이그린정(유한) 5mg
- **Gliclazide**: 디아미크롱80mg, 30mg MR
- **Glimepiride**: 아마릴 1mg, 2mg, 4mg (Dose reduction!!!)

Oral hypoglycemic agents: Meglitinide

Meglitinides	
Repaglinide	If GFR <30 mL/min/1.73 m² start conservatively at 0.5 mg with meals
Nateglinide	If GFR <30 mL/min/1.73 m² start conservatively at 60 mg with meals

- **Repaglinide (novonorm)**
  - Metabolized by the liver, with less than 10 percent renally excreted
  - Starting with a dose of 0.5 mg
- **Nateglinide (fastic)**
  - Hepatically metabolized, with renal excretion of active metabolites
  - Accumulation with reduced renal function
  - Risk of hypoglycemia, not as safe as repaglinide

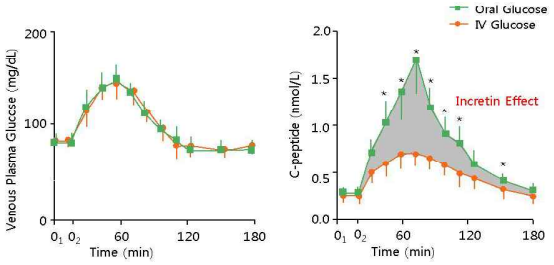
Oral hypoglycemic agents: Metformin

Biguanides	
Metformin***	United States FDA label states, "do not use if SCr ≥1.5 mg/dL in men, ≥1.4 mg/dL in women" British National Formulary and the Japanese Society of Nephrology recommend cessation if eGFR <30 mL/min/1.73 m²

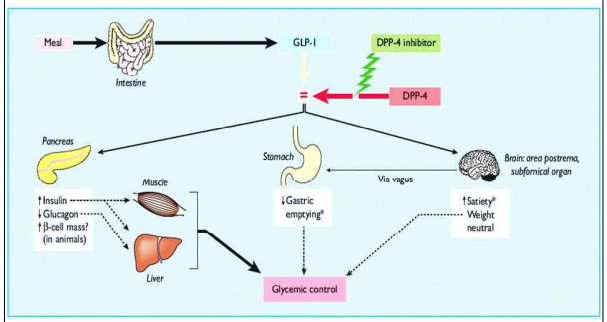
- **Not recommended**
  - metformin is excreted by kidney
  - metformin should not be used in dialysis patients because of an increased risk of lactic acidosis
  - metformin may be used among patients with an eGFR >45 mL/min

Incretin Effect

the Response to Oral versus IV Glucose



Mean ± SE; N=6; *p≤.05; 0_1-0_2=glucose infusion time.
Nauck MA, et al. *J Clin Endocrinol Metab.* 1986;63:492-498. Copyright 1986, The Endocrine Society ©.



DPP-IV inhibitor (gliptin)

- **Sitagliptin (자누비아)**
- **Vildagliptin (가브스)**
- **Linagliptin (트라젠타)**
- **Saxagliptin (온글라이자)**
- **Zemigliptin (제미글로)**

- **Mechanism**
  - glucose level dependent insulin secretion
- **Advantages**
  - no hypoglycemia
  - neutral body weight
- **Disadvantages & cautions**
  - only limited data
  - nasal stiffness
  - angioedema ?
  - pancreatitis?
  - pancreatic cancer?
- **CV event ?**
  - might be beneficial or neutral ?
  - need more RCTs

Dipeptidyl peptidase-IV (DPP-IV) inhibitors

DPP-4 inhibitor	
Sitagliptin	GFR ≥50 mL/min/1.73 m²: 100 mg daily GFR 30-50 mL/min/1.73 m²: 50 mg daily GFR <30 mL/min/1.73 m²: 25 mg daily
Saxagliptin	GFR ≥50 mL/min/1.73 m²: 5 mg daily GFR ≤50 mL/min/1.73 m²: 2.5 mg daily
Linagliptin	No dose adjustment
Vildagliptin**	GFR ≥50 mL/min/1.73 m²: 50 mg twice daily GFR <50 mL/min/1.73 m²: 50 mg daily

- **Linagliptin**
  - only minimally excreted in the urine (<10 percent)
  - does not require dose adjustment in patients on dialysis
  - but, its use in ESRD patients is limited

Incretin mimetics

Incretin mimetic	
Exenatide	Not recommended in GFR <30 mL/min/1.73 m²
Liraglutide	Not recommended in GFR <60 mL/min/1.73 m²

- **Exenatide should not be used**
  - Excreted by the kidneys
  - Clearance is reduced with a GFR decrement
  - Associated with acute kidney injury or acceleration of CKD progression in case reports.

Thiazolidinediones: Pioglitazone

Thiazolidinediones	
Pioglitazone	No dose adjustment
Rosiglitazone	No dose adjustment

- HD does not affect the pharmacokinetics of these drugs
- **Problems of TZDs**
  - Risk of edema formation & heart failure
  - Possible increased mortality with rosiglitazone
  - PPAR gamma-mediated sodium reabsorption by renal epithelial sodium channels in the distal tubule
  - Increased fracture

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors	
Acarbose	Avoid if GFR <30 mL/min/1.73 m²
Miglitol	Avoid if GFR <25 mL/min/1.73 m²

- Not recommended
- Acarbose
  - Serum levels of the drug and its metabolites increase significantly with reduced kidney function,
- Miglitol
  - Greater systemic absorption and undergoes kidney excretion

투석환자에서 사용 가능한 경구 당뇨약

사용가능

- **SU**
  - Glipizide
  - Gliclazide
  - Glimepiride
- **DPPIV-inhibitor**
  - Sitagliptin
  - Vildagliptin
  - Linagliptin
  - Saxagliptin
- **TZD**
  - Pioglitazone
- **Meglitinide**
  - Repaglinide

금기

- **Metformin**
- **Alpha-glucosidase inhibitors**
  - Acarbose
  - Miglitol
- **Incretin mimetics**
  - Exenatide
  - Liraglutide

HD(N=12), only insulin, dailysate glucose 100mg/dL

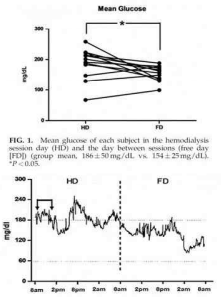


FIG. 1. Mean glucose of each subject in the hemodialysis session day (HD) and the day between sessions (free day [FD]) (group mean, 186 ± 50 mg/dL vs. 154 ± 25 mg/dL). *P < 0.05.

FIG. 5. The 48-h pattern of mean glucose of the whole group of diabetes patients on hemodialysis. Arrows indicate the dialysis period; 180 mg/dL and 60 mg/dL levels are indicated by dotted line. HD, hemodialysis session day; FD, the day between sessions (free day [FD]).

VS

HD(N=17), OAD±insulin, dailysate glucose free

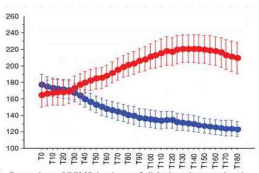


Table 2. Comparison of CGMS data in type 2 diabetic patients on chronic haemodialysis according to the day with or without dialysis session

	Day with dialysis session	Day without dialysis session	P-value[a]
RAD (%)	7.0 ± 5.2	9.0 ± 5.6	0.360
Mean glucose CGMS (mg/dL)	164 ± 43	176 ± 46	0.113
AUC glucose (mg/dL × 24 h)	3850 ± 1073	4113 ± 1130	0.062
Time <70 mg/dL (h/day)[b]	0.6 (0–5.2)	0.3 (0–2.2)	0.169
Time >180 mg/dL (h/day)[b]	7.8 (1.1–23.4)	8.7 (0.4–24)	0.487
Glycaemic variability SD of glucose (mg/dL)	48 ± 24	52 ± 20	0.347

투석환자의 특별한 상황

- Do not maintain the usual mealtime
- No physical activities
- Medical procedure with stress
- Activation of counter-regulatory hormones
- Improvement of insulin resistance after HD

- Dialysate glucose concentration (free, 100mg/dL..)
- Characteristics of dialyzer, Flux
- MW of insulin: 5808 Da

제품명	제조사	용량 (L)	약가	조성									기타
				염화칼슘	염화마그네슘	염화소듐	염화포타슘	아세트산염			구연산염	포도당	
								소듐아세테이트	아세트산	무수아세트산			
보령제오시스-1액	보령제약	5	7,214	45	26.5	1012.5	32.5	143	0	0	0	0	
아트스톰씨엔	케이엘디	10	10,742	64.3	35.6	2107	52.2	0	63.1	0	0	350	
케이바이카드761	한국갑브로솔루션	10	13,428										
케이바이카드294	한국갑브로솔루션	10	13,428	90	35.6	2107	52.2		63.1	0	0	350	
디아하액스액0.15%1호액	대한약품공업	10	12,011	64.3	35.6	2189	52.2	381.5	0	0	0	525	
헤모비액스0.15%1호액	중외제약	10	13,346										
다이아알리드에이산0.1%	보령제약	10	10,304										
에취디플-비씨지액(A액)	한국갑브로솔루션	10	12,114	77.2	35.6	2127	52.2	285.3	0	0	0	0	
디에취액스액0.1%	대한약품공업	10	12,177										
헤모비액스0.1%1호액	중외제약	10	12,881										
아트스톰지액10L	케이엘디	10	10,304										
보령헤모시스지액(A액)	보령제약	10	12,219	77.2	35.6	2127	52.2	0	0	172	0	0	
아트스톰에이액10L	케이엘디	10	9,527										
보령제오시스-1액	보령제약	10	10,821										
에이에취디액(A액)10L	대한약품공업	10	10,821	90	53	2025	65	286	0	0	0	0	
에취디플비씨10L	한국갑브로솔루션	10	11,059										
헤모트하이트비1호	중외제약	10	11,909										
보령헤오시스지액(A액)	보령제약	5	8,146	38.6	17.8	1063.5	26.1	0	0	86	0	175	
에취디플-비씨지액(A액)	한국갑브로솔루션	5	8,076	38.6	17.8	1063.5	26.1	0	0	86	0	175	
크레플에이액10L	대한약품공업	10	13,428	77.2	35.6	2147.7	52.2	0	84.1	0	0	0	
프라플엘에이액10L	대한약품공업	10	13,428	67	14	2148	52	0	63	0	0	0	
프라플지에이액10L	대한약품공업	10	13,428	67	35.6	2148	52.2	0	63	0	0	315.5	
프라플지에이액10L	대한약품공업	10	13,428	77	35.6	2148	52	0	63	0	0	315.5	
씨트라세이트3.0	제이에스엠텔스케어	3.79	5,850	8.13	3.73	172.19 (23.53)	5.49	1.51	0	0	6.19	81.02	
씨트라세이트3.5	제이에스엠텔스케어	3.79	5,850	9.48	3.73	172.19 (23.53)	5.49	1.51			6.19	81.02	
아트스톰 A1	케이엘디	10		77.2	53	2148	65	0	0	0	49	0	중산
아트스톰 A2	케이엘디	10		64.4	35.6	2250	52.2	0	0	0	49	0	중산
아트스톰 G1	케이엘디	10		64.4	35.6	2250	52.2	0	0	0	49	350	중산
아트스톰 G2	케이엘디	10		51.5	17.8	2250	52.2	0	0	0	49	350	중산

Take Home Messages

- 투석 환자의 혈당 조절 목표
  ~7.0-8.0% or ~7.0-9.0%
  (너무 낮지 않게 한다)
- 인슐린 사용을 권장
- 경구약제 사용시에는 사용 가능한 약제 고려
  - glilazide, glipizid, glimepiride
    linagliptin, pioglitazone, repaglitinide,