# Pharmacologic Management in Elderly Diabetes

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'젊은 오빠' 시대



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- 1. Why we are interested in the elderly diabetes?
- 2. What are the characteristics of the elderly diabetes?
- 3. What are the considerations of the elderly diabetes?
- 4. What are the hypoglycemic agents and the cautions of the elderly diabetes?

# Why we are interested in the elderly diabetes?

# 노인 인구 증가 추이

#### 65세 이상기준 단위: 만명, 괄호는 전체 인구 중 비율(%)



# Prevalence of Diabetes

"While the prevalence of diabetes get reach the highest at age of 60~69 in men, it is constantly increasing along the age in women"



Persons (1,000)

Korean Diabetes Fact Sheet 2016

What are the characteristics of the elderly diabetes?

#### Characteristics of Elderly Diabetes



#### Geriatric Syndrome and Elderly Diabetes



**Increased Functional Impairment and Disability** 

Laiteerapong N, et al. Diabetes Care. 2011;34:1749-1753

#### Essential Factors of Assessment of Elderly



Principles of Geriatric Medicine & Gerontology p.100

What are the considerations of the elderly diabetes?

#### Treatment Options of Diabetes



Adapted from: DeFronzo RA. *Diabetes* 2009;58:773–95.

#### Elderly vs Younger



#### Elderly patients = Younger adults

### Treatment Considerations

Elderly patients **≠** Younger adults

Am J Geriatr Pharmacother. 2009;7:324–342

## Glycemic Control

Study	Microvasc		CVD		Mortality	
UKPDS	$\mathbf{\Psi}$	•	<b>←→</b>	•	<b>←→</b>	•
DCCT / EDIC*	Ŷ	♥	<b>~-&gt;</b>	♦	<b>←→</b>	<b>←→</b>
ACCORD	4	>	<del>~</del> •	>	1	
ADVANCE	<b>V</b>		<del>~</del> •	>	<del>(</del> -•	>
VADT	<b>V</b>		<del>&lt;</del> -	>	<del>(</del> -	>

Initial Trial Long Term Follow-up \* in T1DM

Kendall DM, Bergenstal RM. © International Diabetes Center 2009

UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854. Holman RR et al. *N Engl J Med*. 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329;977. Nathan DM et al. *N Engl J Med*. 2005;353:2643. Gerstein HC et al. *N Engl J Med*. 2008;358:2545. Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129. (erratum: Moritz T. *N Engl J Med* 2009;361:1024)

# Consequence of Hypoglycemia



<sup>1</sup>Whitmer RA, et al. *JAMA*. 2009; 301: 1565–1572; <sup>2</sup>Bonds DE, et al. *Br Med J*. 2010; 340: b4909; <sup>3</sup>Barnett AH. *Curr Med Res Opin*. 2010; 26: 1333–1342; <sup>4</sup>Jönsson L, et al. *Value Health*. 2006; 9: 193–198; <sup>5</sup>Foley JE, Jordan J. *Vasc Health Risk Manag*. 2010; 6: 541–548; <sup>6</sup>Begg IS, et al. Can J Diabetes. 2003; 27: 128–140; <sup>7</sup>McEwan P, et al. *Diabetes Obes Metab*. 2010; 12: 431–436.

## Management of Hyperglycemia



ADA Standards of Medical Care in Diabetes-2017

#### 2015 당뇨병 진료지침

# 당뇨병의 특수상황 - 노인당뇨병

- 노인 당뇨병환자에게서 혈당조절 목표는 건강한 성인과 다르지 않으나, 신체 및 인지기능, 여명 등을 고려하여 개별화한다. 그러나 증상이나 급성합병증을 유발할 수 있는 고혈당 또는 저혈당은 피하는 것이 좋다. [E]
- 2. 혈당강하제의 부작용 또는 상호작용에 대한 적극적인 주의가 필요하다. [E]
- 고혈당 이외의 다른 심혈관 위험인자 치료여부는 이를 통해 얻을 수 있는 이득과 환자들의 건강상태 등을 고려해서 결정한다. 치료목표는 젊은 성인과 다르지 않다. [E]
- 당뇨병합병증 선별검사 역시 개별화해야 하며, 특히 기능장애와 관련된 합병증에 주안점을 두는 것이 좋다. [E]
- 5. 노인증후군 개념에서 시청각장애, 영양실조, 근감소, 요실금, 보행장애, 인지 및 정서기능, 신체기능, 다약제사용 등 전반적인 기능을 평가하고 치료에 반영하도록 고려한다. [E]

# HbAlc Goals in Elderly Diabetes(1)

American Geriatr	ics Society <sup>68</sup>	Department of Veterans Affair	'S <sup>69</sup>	American Diabetes Association <sup>8</sup>		European Diabetes Working Older People <sup>9</sup>	g Party for	
Description of		Description of patient				Description of patient		
patient stratum	$HbA_{1c}goal$	stratum	HbA <sub>1c</sub> goal	Description of patient stratum	HbA <sub>1c</sub> goal	stratum	HbA <sub>1c</sub> goal	l
Healthy	7.0-7.5%	None or very mild microvascular complications; life expectancy of 10-15 year	<7.0%	Healthy (few coexisting chronic illnesses; intact cognitive and functional status)	<7.5%	Without major comorbidities	7.0-7.5%	
Moderate comorbidities	7.5-8.0%	Long duration of diabetes (>1) years); requires combination drug regimen including insuli	<8.0%	Complex/intermediate (examples: multiple coexistin chronic illnesses*, ≥2 instrumental ADL impairments, or mild-moderate cognitive impairment)	<8.0%	Frail patients (dependent; multi-system disease; care home residency, including	7.6-8.5%	J
Multiple comorbidities	8.0-9.0%	Advanced microvascular complications and/or major comorbid illness; life expectancy <5 years	8.0-9.0%	Very complex/poor health (examples: long term care, end stage chronic illnesses†, moderate-severe cognitive impairment, or ≥2 ADL dependencies)	<8.5%‡	those with dementia)		
ADL=activities of d	aily living.							

BMJ 2016;353:i2200

# HbAlc Goals in Elderly Diabetes(2)

- CATEGORY 1: FUNCTIONALLY INDEPENDENT : HbA1c target : 7.0~7.5%
- CATEGORY 2: FUNCTIONALLY DEPENDENT Sub-category A: Frail
  HbA1c target : ~8.5% Sub-category B: Dementia
  HbA1c target : ~8.5%
- CATEGORY 3: END OF LIFE CARE
  - glycemic target : avoid hypoglycemia, individualized therapy

IDF Global Guideline for Managing Older People with Type 2 Diabetes 2013

What are the hypoglycemic agents and the cautions of the elderly diabetes?

### Glucose-lowering Medications



# Insulin

# Characteristics of Insulin

A1c lowering effects	1.5~3.5%
Advantages	Proven effects No dose limitation
Disadvantages	Need a parenteral injection Frequent hypoglycemia Weight gain Need glucose monitoring and adjusting the dose accordingly Require patient's executive functioning

### Insulin Preparations

Activity/ Brand Name	Generic Name	Туре	Onset of action	Peak Activity, h	Duration, h	Compatibility	
Rapid acting							
Humalog Novorapid Apidura	Insulin lispro Insulin aspart Insulin glulisine	Insulin analogue Insulin analogue Insulin analogue	15 min 15 min 15 min	0.5~1.5 1-3 0.5-1	3-5 3-5 3	NPH insulin NPH insulin NPH insulin	
Short acting							
Humulin R	Regular insulin	Regular insulin	0.5~1 h	2.5~5	8~12	NPH insulin	
Intermediate acti	ing						
Humulin N and Novolin N	Isophane insulin	Isophane insulin	1~1.5 h	4~12	10~24	Insulin analogues, Regular insulin	
Long acting	Long acting						
Lantus Levemir	Insulin glargine Insulin detemir	Long acting insulin analogue	1.1 h 1-2 h	None 6~8	24 (dose dependent)	None None	
Premix type							
Humulin 70/30	70% Isophane insulin/30%	Combination of NPH and	30 min	1.5~16	10~24	None	
Novomix 70/30	70% Aspart protamine/30%	Combination of NPH-like	15 min	1~4	10~24	None	
Humalog Mix	75% Lispro protamine/25%	Combination of NPH-like	15 min	1~6.5	10~24	None	
Humalog mix	50% Lispro protamine/50%	Combination of NPH-like	15 min	1~6.5	10~24	None	
Novomix 50/50	50% Aspart protamine/50% aspart insulin	Combination of NPH-like and rapid-acting insulin	15 min	1~4	10~24	None	

#### Am J Geriatr Pharmacother. 2009;7:324–342

#### Before instituting Insulin therapy

- Visual acuity
- Manual dexterity
- Cognitive function
- Caregiver status
- Financial ability to afford insulin
- Insulin-delivery supplies

#### Caveats in the Older Population

- Long acting insulin(basal insulin)
  - : injection time & dose
    - $\rightarrow$  consider glucose pattern
    - $\rightarrow$  postprandial > fasting hyperglycemia
      - ; starting basal insulin in the morning
- Pre-mix insulin
  - : meal time fixed
    - $\rightarrow$  prevention of hypoglycemia

The Joslin Guideline for the Care of the Older Adult with Diabetes 2015

#### Insulin Secretagogues : SU & Meglitinide

# Characteristics of SU

A1c lowering effects	1.0~2.0%
Advantages	Proven glucose lowering efficacy Long-term clinical experiences Relatively low cost
Disadvantages	Frequent hypoglycemia Weight gain Contraindicated in severe liver or renal disease

Adrenergic-blocking agents	Advanced age
Alcohol consumption	Autonomic neuropathy
Cognitive impairment	Complex drug regimens
Endocrine deficiency (thyroid, adren	al, pituitary)
Hepatic dysfunction	Hypoglycemia unawareness
Intercurrent illness	Polypharmacies
Poor nutrition	Recent hospitalization
Renal Insufficiency	Secretagogues/insulin
Sedative agents	Tight glycemic control

Drugs Aging. 2004;21:511–530, Cleve Clin J Med. 2008;75:70–78

### Characteristics of Meglitinide

A1c lowering effects	0.5-1%
Advantages	Rapid onset of action time Flexible dosing for those with irregular eating habits
Disadvantages	Hypoglycemia Weight gain Frequent dosing Relatively high cost Avoid under 30 ml/min of CCR

### Insulin Sensitizers : Biguanides & Thiazolidinediones

# Metformin : action mechanism



# Characteristics of Metformin

A1c lowering effects	1.0-2.0%
Advantages	Proven effectiveness as the first-line therapy Low risk of hypoglycemia Neutral effect on weight Long-term clinical experiences Low cost
Disadvantages	Contraindicated when serum creatinine $\geq 1.5 \text{ mg/dL}$ in men or $\geq 1.4 \text{ mg/dL}$ in women, liver failure, and advanced heart failure GI side effects may cause poor appetite and malnutrition Concerns of vitamin B12 and folate deficiency

# TZD : action mechanism



N Engl J Med. 2004; 351:1106–1118

# Characteristics of TZD

A1c lowering effects	0.5-1.4%
Advantages	Reduce insulin resistance Durable effects on glycemic control Low risk of hypoglycemia
Disadvantages	Weight gain Fluid retention, which may exacerbate underlying heart failure Increased risk of bone fractures

Diabetes Metab J 2012;36:336-344

### TZD and Heart failure

Absolutely contraindication in patients with class III or IV heart failure

#### Risk factors for TZD-associated Heart Failure

Age > 70 years S-Cr > 2.0 mg/dL Weight gain or development of edema while taking a TZD Treatment with loop diuretics Use of insulin Left ventricular hypertrophy Presence of aortic or mitral valve heart disease

#### The Insulin Resistance Intervention after Stroke (IRIS) Trial



Kernan WN, et al.N Engl J Med. 2016 Apr 7;374(14):1321-31

# a-glucosidase inhibitors

# Characteristics of $\alpha$ -GI

A1c lowering effects	0.5-0.8%
Advantages	Effectively reduce postprandial glucose No hypoglycemia
Disadvantages	Frequent GI side effects Frequent dosing Relatively high cost $CrCl \leq 24$ mL/min : not recommended Contraindicated in cirrhosis

*Diabetes Metab J 2012;36:336-344 Am J Geriatr Pharmacother. 2009;7:324–342* 

#### Incretin : GLP-1 A & DPP-IV I

## Incretin : action mechanism



#### The glucose-dependent mechanism of DPP-4 inhibitors targets 2 key defects

#### : insulin release and unsuppressed hepatic glucose production.

Adapted from Brubaker PL, Drucker DJ *Endocrinology* 2004;145:2653–2659; Zander M et al *Lancet* 2002;359:824–830; Ahrén B *Curr Diab Rep* 2003;3:365–372; Buse JB et al. In *Williams Textbook of Endocrinology*. 10th ed. Philadelphia, Saunders, 2003:1427–1483.

#### **Incretin :** GLP-1 Agonists and DPP IV inhibitors



Currently approved for useInvestigational compound

## Characteristics of GLP-1 Agonist

A1c lowering effects	0.5-1.0%
Advantages	Low risk of hypoglycemia Weight reduction (beneficial in obese patients) Once weekly fomulations Decreasein dose of SU or insulin
Disadvantages	Relatively high cost Need a parenteral injection GI side effects may not be tolerated in some older patients High cost Limited long-term experience

*Diabetes Metab J 2012;36:336-344* The Joslin *Guideline for the Care of the Older Adult with Diabetes 2015* 

### Characteristics of DPP-IV Inhibitor

A1c lowering effects	0.5-0.8%
Advantages	Control postprandial glucose Low risk of hypoglycemia Weight neutrality Good drug for frail elderly
Disadvantages	only mild to moderate lowering of A1c by 0.5-0.8% Relatively high cost

*Diabetes Metab J 2012;36:336-344* The Joslin *Guideline for the Care of the Older Adult with Diabetes 2015* 

#### Clinical Guideline about DPP-IV Inhibitor

2009 Clinical Guidance from UK National Institute for Health and Clinical Excellence

Considering **DPP-4** inhibitors rather than SUs as second-line therapy after first-line metformin in patients who are at high risk for hypoglycemia or its consequences for example older adults with hazardous jobs (eg, working at heights, working with heavy machinery) and those who live alone

European Diabetes Working Party for Older People 2011 Clinical Guidelines for Type 2 Diabetes Mellitus

Consider a **DPP-4 inhibitor** as an add-on to metformin when use of a sulphonylurea may pose an unacceptable **hypoglycemia risk** in an older patient with diabetes

> http://www.nice.org.uk/CG87shortguideline. Accessed July 3, 2009, Diabetes & Metabolism, 2011:37;S27-S38

#### TECOS safety trial



Green JB et al. N Engl J Med. 2015; Jun 8.

#### Sodium-Glucose cotransporter 2 Inhibitor

### SGLT-2 Inhibitor : action mechanism



#### Characteristics of SGLT-2 Inhibitor

A1c lowering effects	0.6-0.8%
Advantages	Low risk of hypoglycemia Decreasing Weight & blood pressure CV safety
Disadvantages	Increase incidence of genitourinary tract infection Caution : renal impairment loop diuretics low body weight

*Curr Med Res Opin.* 2012;28(7):1173–1178 *Ann Med.* 2012;44(4):375–393



#### PROFILES OF ANTIDIABETIC MEDICATIONS



	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU GLN	COLSVL	BCR-QR	INSULIN	PRAML	
нүро	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/ Severe Mild	Neutral	Neutral	Moderate to Severe	Neutral	
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss	
RENAL/ GU	Contra- indicated CKD Stage 3B,4,5	Exenatide Not In dicated CrCl < 30	Not Effective with eGFR < 45 Genital Mycotic Infections	Dose Adjustment Necessary (Except Linagliptin)	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral	
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate	
	Neutral	Noutral Possi	Possible	Noutral	Noutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral	
ASCVD	Benefit	Neutra	Benefit	Neduar	Neutrai	Neutral	?	Neutian	Safe	Nearta	riediral	
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral	
Few adverse events or possible benefits Use with caution Likelihood of adverse effects ? Uncertain effect												

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#### Glucose-lowering algorithm for frail patients with T2DM



European Diabetes Working Party for Older People / Diabetes & Metabolism 37 (2011) S27-S38

#### Conceptual model of Personalized Decision Support



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### Thank you for your attention !!

#### Geriatric Syndrome and Elderly Diabetes

