Oral Anti-diabetic Drugs in Older Adults with Diabetes

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How old is The Old Man?

- 70~74 years: 53%
- 65~69 years: 28.1%
- 60~64 years: 8.8%
- 75~79 years: 4.6%
- Over 80 years: 2.8%
- Others: 2.7%

Total number: 1000 person

Sourced by KIHASA
Agenda

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 oral hypoglycemic agents and the cautions of the elderly diabetes?
Why we are interested in the elderly diabetes?
Proportion of elderly people in the World

Old-age dependency ratio in 2030

Ratio of population aged 65+ per 100 population aged 15-64:
- No data
- Less than 10
- 10 - 19.99
- 20 - 29.99
- 30 - 39.99
- 40 - 49.99
- 50 or more
Prevalence of Korean diabetic patients according to the gender and age

![Bar chart showing the prevalence of Korean diabetic patients by age and gender. The chart indicates a higher prevalence in older age groups, with a significant increase in the over 80 age group for both males and females.](Image)
What are the characteristics of the elderly diabetes?
Pathogenesis of hyperglycemia in elderly patients

Factors Predisposing the Elderly to Diabetes

- Coexisting Illness
- Genetics
- Drugs
- Decreased physical activity
- Age-related Decreased Insulin secretion
- Age-related Insulin resistance
- Adiposity

Comprehensive Physiology
Characteristics of elderly diabetes

- Rare typical Sx
- Frequent Atypical Sx
  - urinary incontinence, falling, infection etc
- Hypoglycemia increase
- Cognitive function decrease
- Heterogeneity
- Concomitant disease
Treatment goal for elderly diabetes

- Control of Hyperglycemia and its symptoms
- Prevention, evaluation and treatment of macrovascular and microvascular complications of DM
- DM self-management through education
- Maintenance or improvement of general health status

Essential factors of assessment of elderly

- Cognitive
- Medical
- Affective
- Environmental
- Economic
- Social Support
- Spirituality

Functional Status

Principles of Geriatric Medicine & Gerontology p.100
Geriatric syndrome and elderly diabetes

Typical Geriatric Syndromes

- Depression or Low well-being
- Functional Disability
- Falling
- Cognitive impairment
- Malnutrition
- Urinary incontinence

Diabetic micro- and macrocomplications

Comorbid illness

Lack of social support

Aging

Individualization

Hypoglycemia

Mortality

Hyperglycemia

What are the considerations of the elderly diabetes?
Treatment Options for T2DM

* Tolbutamide, chlorpropamide, glibenclamide, gliclazide, glipizide

<table>
<thead>
<tr>
<th>Year</th>
<th>People (Million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1957</td>
<td>150</td>
</tr>
<tr>
<td>1960</td>
<td>200</td>
</tr>
<tr>
<td>1965</td>
<td>250</td>
</tr>
<tr>
<td>1970</td>
<td>300</td>
</tr>
<tr>
<td>1990</td>
<td>200</td>
</tr>
<tr>
<td>2000</td>
<td>250</td>
</tr>
<tr>
<td>2005</td>
<td>300</td>
</tr>
<tr>
<td>2010</td>
<td>350</td>
</tr>
</tbody>
</table>

- Sulphonylureas* since 1957
- Metformin (US)
- Acarbose
- Glimepiride
- Nateglinide
- Repaglinide
- GLP-1, Exendin
- PPARγ + α agonists
- Pramlintide
- Miglitol, Voglibose
- Rosiglitazone, Pioglitazone
- Sitagliptin, Vildagliptin
- Gene Therapy

* Tolbutamide, chlorpropamide, glibenclamide, gliclazide, glipizide
Relative Merits of Hypoglycemic Agents

Decrease in HbA1c: Potency of Monotherapy

HbA1c %

-2.5

-2

-1.5

-1

-0.5

0

AGI

Cycloset

Welchol

DPPTV inh

Pramlintide

Exenitide

TZD

SU/GLIN

Metformin

Insulin

2011 71st ADA Current Issue
Treatment with T2DM

Pharmacologic Options

Elderly patients = Younger adults

Treatment Considerations

Elderly patients ≠ Younger adults

## Glycemic control

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UKPDS</strong></td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>*<em>DCCT / EDIC</em></td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td><strong>ACCORD</strong></td>
<td>↓</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td><strong>ADVANCE</strong></td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td><strong>VADT</strong></td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

* in T1DM

Kendall DM, Bergenstal RM. © International Diabetes Center 2009

Management of hyperglycemia

<table>
<thead>
<tr>
<th>Risk/Feature</th>
<th>More stringent</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia, other adverse events</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Disease duration</td>
<td>Newly diagnosed</td>
<td>Long-standing</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>Absent</td>
<td>Few / mild</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>Absent</td>
<td>Few / mild</td>
</tr>
<tr>
<td>Resources, support system</td>
<td>Readily available</td>
<td>Limited</td>
</tr>
</tbody>
</table>

ADA Standards of Medical Care in Diabetes-2014
Target of HbA1c in elderly diabetes

- **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*
## Target in elderly diabetes

<table>
<thead>
<tr>
<th>Patient characteristics/health status</th>
<th>Rationale</th>
<th>Reasonable A1C goal (A lower goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden)</th>
<th>Fasting or preprandial glucose (mg/dL)</th>
<th>Bedtime glucose (mg/dL)</th>
<th>Blood pressure (mmHg)</th>
<th>Lipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>Longer remaining life expectancy</td>
<td>&lt;7.5%</td>
<td>90–130</td>
<td>90–150</td>
<td>&lt;140/80</td>
<td>Statin unless contraindicated or not tolerated</td>
</tr>
<tr>
<td>Complex/intermediate</td>
<td>Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk</td>
<td>&lt;8.0%</td>
<td>90–150</td>
<td>100–180</td>
<td>&lt;140/80</td>
<td>Statin unless contraindicated or not tolerated</td>
</tr>
<tr>
<td>Very complex/poor health</td>
<td>Limited remaining life expectancy makes benefit uncertain</td>
<td>&lt;8.5%†</td>
<td>100–180</td>
<td>110–200</td>
<td>&lt;150/90</td>
<td>Consider likelihood of benefit with statin (secondary prevention moreso than primary)</td>
</tr>
</tbody>
</table>

*Multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild to moderate cognitive impairment

**Long-term care or end-stage chronic illnesses or moderate to severe cognitive impairment or 2+ ADL dependencies

†Individual may benefit from an A1C goal lower than 8.5%
What are the oral hypoglycemic agents and the cautions of the elderly diabetes?
Drug Groups

OHA

- Insulin secretagogues
  - Sulfonylureas
  - Meglitinide analogue
- Insulin sensitizer
- α-glucosidase inhibitors
- Dipeptidyl Peptidase-IV inhibitors
- Sodium-glucose cotransporter-2 inhibitor

- Biguanides
- Thiazolidinediones (TZD)
Insulin Secretagogues:
SU & Meglitinide
Insulin Secretagogues

- Insulin exocytosis
- Glucose
- Ca++
- Opening of voltage-dependent Ca^{2+} channel
- ATP
- Closure of ATP-sensitive K^+ channel
- Depolarization
Sulfonylurea

- Mainstay of Treatment for T2DM
- Main Side Effects: Hypoglycemia and Weight gain

**Risk factors of Hypoglycemia on older adults**

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

# Pharmacological characteristics of SU

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose range (mg)</th>
<th>Duration (hr)</th>
<th>Dosage/day (T)</th>
<th>Metabolism/Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>500-3,000</td>
<td>6-12</td>
<td>2-3</td>
<td>Hepatic with renal excretion</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>100-500</td>
<td>24-72</td>
<td>1</td>
<td>Renal excretion(30%), some hepatic metabolism</td>
</tr>
<tr>
<td><strong>Second generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td>2.5-40</td>
<td>16-24</td>
<td>1-2</td>
<td>Hepatic, renal excretion of inactive metabolites</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>1.25-20</td>
<td>12-24</td>
<td>1-2</td>
<td>Hepatic, renal excretion of inactive metabolites</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>1-8</td>
<td>12-24</td>
<td>1</td>
<td>Hepatic with renal excretion of active metabolites</td>
</tr>
<tr>
<td>Gliquidone</td>
<td>15-60</td>
<td>8-10</td>
<td>1-2</td>
<td>Hepatic with renal excretion of inactive metabolites</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>40-320</td>
<td>10-15</td>
<td>1-2</td>
<td>Hepatic with renal excretion of inactive metabolites</td>
</tr>
</tbody>
</table>

*J Nephrol 2010;23(Suppl15):S72-S79*
CV outcome of Sulfonylurea

Comparative Effectiveness of Sulfonylurea and Metformin Monotherapy on Cardiovascular Events in Type 2 Diabetes Mellitus: A Cohort Study

Sulphonylurea monotherapy for patients with type 2 diabetes mellitus

Sulphonylureas are widely used for patients with type 2 diabetes mellitus. Sulphonylureas lower blood glucose by stimulating insulin secretion from the pancreas thereby increasing the insulin levels in the blood. Seventy-two trials were included in the systematic review assessing the effects of sulphonylurea as sole therapy versus other comparators in patients with type 2 diabetes mellitus. A total of 22,589 participants were included. The number of participants randomised to a sulphonylurea was 9707 and the number of participants randomised to a comparator was 12,805. The duration of the interventions varied from 24 weeks to 10.7 years. All trials had deficiencies (risk of bias) and for the individual comparisons the number of participants were small, resulting in a high risk of random errors (play of chance). Data on mortality and diabetic complications were sparse and inconclusive due to adverse events were more common with alpha-glucosidase inhibitors (for example acarbose) compared with second-generation sulphonylureas (for example glibenclamide, glipizide, glibornuride and gliclazide), but the data were sparse. Severe hypoglycaemia was more common with second-generation sulphonylureas compared with metformin and thiazolidinediones (for example pioglitazone), but again the data were sparse. Due to lack of data we could not adequately evaluate health-related quality of life and costs. There is insufficient evidence regarding patient-important outcomes from high-quality randomised controlled trials (RCTs) to support the decision as to whether to initiate sulphonylurea as sole therapy. Large-scale and long-lasting randomised clinical trials with low risk of bias, which focus on mortality, diabetic complications, adverse events and health-related quality of life, are needed.

- **second-generation sulfonylureas**
  - selective for the pancreatic sulfonylurea receptors
  - toxicity of older sulfonylureas on ATP-dependent potassium channels on cardiac cells and coronary vessels

*The Cochrane Library* 2013, Issue 4
Diabetes, Metabolic Syndrome and Obesity 2014:7 391–400
# Meglitinide

- Rapid-acting insulin secretagogues
- Avoid under 30 ml/min of CCR

<table>
<thead>
<tr>
<th>Drug</th>
<th>Repaglinide, Nateglinide, Mitiglinide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Action Mechanism</strong></td>
<td>Release of insulin from pancreatic β-cell</td>
</tr>
<tr>
<td><strong>Dosing in Elderly</strong></td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>0.5-4 mg 30 min before each meal</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>60-120 mg 30 min before each meal</td>
</tr>
<tr>
<td>Mitiglinide</td>
<td>10 mg 30 min before each meal</td>
</tr>
</tbody>
</table>

**Geriatric Considerations**

May be helpful in those with **irregular eating habits**

Insulin Sensitizers:
Biguanides & Thiazolidinediones
Metformin addresses key endocrine defects in the pathophysiology of type 2 diabetes.

- **Pancreas**: Impaired Insulin secretion
  - Reduced by metformin
- **Liver**: Increased glucose production
  - Reduced by metformin
- **Muscle**: Decreased glucose uptake
  - Increased by metformin
- **Fat**: Increased lipolysis
  - Increased by metformin

**Hyperglycaemia** is at the center, indicating its role in connecting these processes.
Clinical outcomes in overweight Pts in the UKPDS

Any diabetes-related endpoint

Metformin (n=342)
Conventional (n=411)

Intensive (n=951)

Met vs. conventional: p=0.0023
Met vs. intensive: p=0.0034

Consideration of Metformin

- **Common side effects**
  - GI upset, diarrhea, anorexia, weight loss
  - Vitamin $B_{12}$ deficiency
  - Lactic acidosis

- **No candidates**
  - frail, anorexic, underweight, CHF, renal or hepatic insufficiency or dehydration

- **Contraindication**
  - $S\text{-Cr} \geq 1.5 \text{ mg/dl} (\text{men}), \geq 1.4 \text{ mg/dl} (\text{women})$
  - $CrCl < 60 \text{ mL/min}$

Effects of TZD on Insulin Sensitivity

Liver → TZD → Insulin resistance → Muscle → TZD → Adipose tissue

↑ Glucose output

↓ Glucose uptake

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

TZD and Fracture risk

A Diabetes Outcome Progression Trial (ADOPT)

Diabetes Care. 2008;31:845–851
Geriatric Considerations of TZD

- CHF exacerbation
- Potential CV risk
- Risk of edema
- Weight gain
- Increased fracture risk
- CHF increased at higher doses and with insulin

Am J Geriatr Pharmacother. 2009;7:324-342
α-glucosidase inhibitors
### **α-glucosidase inhibitor**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acarbose. Voglibose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Action Mechanism</strong></td>
<td>Competitive and reversal inhibition of intestinal α-glucosidase hydrolase and pancreatic amylase</td>
</tr>
<tr>
<td><strong>Dosing in the Elderly</strong></td>
<td></td>
</tr>
<tr>
<td>Acarbose</td>
<td>Initiate at 25 mg, titrated in 25-mg, increments q 4-8wk to max. of 50-100mg</td>
</tr>
<tr>
<td>Weight ≤ 60 kg: maximum 50 mg/meal</td>
<td></td>
</tr>
<tr>
<td>Weight &gt; 60 kg: maximum 100 mg/meal</td>
<td></td>
</tr>
<tr>
<td><strong>Use in Renal Impairment</strong></td>
<td>CrCl ≤ 24 mL/min : not recommended</td>
</tr>
<tr>
<td><strong>Use in Hepatic Impairment</strong></td>
<td>Contraindicated in cirrhosis</td>
</tr>
<tr>
<td><strong>Common AEs</strong></td>
<td>Flatulence, diarrheas, GI upset, increased LFT</td>
</tr>
<tr>
<td><strong>Geriatric consideration</strong></td>
<td>Minimal risk of hypoglycemia</td>
</tr>
</tbody>
</table>

> **CAUTION !!!**

: concurrent *prandial insulin or insulin secretagogues*

Dipeptidyl Peptidase-IV inhibitors
The glucose-dependent mechanism of DPP-4 inhibitors targets 2 key defects:

- insulin release and unsuppressed hepatic glucose production.

Incretin:
GLP-1 Agonists and DPP-IV inhibitors

**GLP-1 receptor agonist**
- Parenteral peptide
- Direct agonist of GLP-1R
- Pharmacologic levels GLP-1 agonist

**DPP-IV inhibitors**
- Orally administered
- Inhibit degradation of incretins
  - ‘Restores’ physiological levels of GLP-1 and GIP

**GLP-1 backbone**
- LY2189265
- Albiglutide
- Semaglutide
- Weekly
- QD-BID
- Liraglutide

**Exendin-4 backbone**
- Weekly
- Exenitide QW
- CJC-1134-PC
- Lixisenitide

**DPP-IV inhibitors**
- Sitagliptin
- Vildagliptin
- Saxagliptin
- Alogliptin
- Linagliptin

• Currently approved for use
• Investigational compound

2011 71th ADA Current Issue
## Considerations of DPP-IV inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sitagliptin, Vildagliptin</th>
</tr>
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<tbody>
<tr>
<td><strong>Dosing in the Elderly</strong></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>100 mg/d</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>100 mg/d</td>
</tr>
<tr>
<td><strong>Use in Renal Impairment</strong></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>CrCl 30-50 mL/min : 50mg/d</td>
</tr>
<tr>
<td></td>
<td>CrCl ≤ 30 mL/min : 25 mg/d</td>
</tr>
<tr>
<td><strong>Use in Hepatic Impairment</strong></td>
<td>No adjustment required</td>
</tr>
<tr>
<td><strong>Common AEs</strong></td>
<td>Headache, Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td><strong>Geriatric consideration</strong></td>
<td>Minimal reisk of hypoglycemia, weight neutral</td>
</tr>
</tbody>
</table>

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

SAVOR-TIMI: more patients receiving saxagliptin were hospitalized for heart failure compared to placebo.

Sodium-glucose cotransporter 2 Inhibitor
Normal renal glucose handling

Majority of glucose is reabsorbed by SGLT2 (90%)

Remaining glucose is reabsorbed by SGLT1 (10%)

Minimal to no glucose excretion

SGLT, sodium-glucose co-transporter.

Action mechanism of SGLT-2 Inhibitor

- Increases urinary volume by only ~1 additional void/day (~375 mL/day) in a 12-week study of healthy subjects and patients with Type 2 diabetes.

SGLT-2 inhibitor

- **Benefit**
  - ✓ Low incidence of hypoglycemia
  - ✓ Decreasing weight & blood pressure

- **Main side effect**
  - ✓ Increase incidence of genitourinary tract infection

- **Geriatric consideration**
  - ✓ Caution
    - Renal impairment patient (GFR < 60 ml/min/1.73 m²)
    - Loop diuretic user
    - Low body weight

*Curr Med Res Opin. 2012;28(7):1173–1178*
glucose-lowering algorithm for frail patients with T2DM

Recommended glucose targets:
Fasting glucose range = 7.6-9.0 mmol/L, HbA1c range = 7.6-8.5%

3-6 months dietary and lifestyle advice

Not achieving agreed glucose targets

Frailty criteria:
Care home residence
Significant cognitive decline
Major lower limb mobility disorder
History of disabling stroke

Metformin contraindicated in renal/hepatic dysfunction, respiratory/heart failure, anorexia, gastrointestinal disease

Metformin

Alternative treatments:
DPPIV inhibitors or Lower risk sulphonylurea (SU), Glinide

Failure to achieve glucose targets

Further weight loss with a GLP-1 agonist may have adverse consequences in a frail patient

Metformin + DPPIV inhibitor

Alternative treatments:
Metformin + Lower risk SU, Metformin + GLP-1 agonist

Failure to achieve glucose targets

Finally associated with increased hypoglycemia risk: caution when using insulin or sulphonylurea therapy

Metformin + insulin

Alternative treatments:
Lower risk SU + insulin

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

➢ Individualization

➢ Start low and Go slow
Thank you for your attention!!