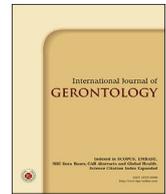




Contents lists available at ScienceDirect

International Journal of Gerontology

journal homepage: www.ijge-online.com

Review Article

Blood Glucose Management of Type 2 Diabetes in the Older People[☆]Wei-Che Chen^{a,*}, Chun-Chua Lee^a, Ming-Nan Chien^a, Sung-Chen Liu^a,
Chao-Hung Wang^a, Wei-Shiung Yang^{b,c}^a Division of Endocrine, Department of Internal Medicine, Mackay Memorial Hospital, Taipei, Taiwan, ^b Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan, ^c Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

ARTICLE INFO

Article history:

Received 7 February 2018

Received in revised form

17 April 2018

Accepted 29 May 2018

Available online 21 June 2018

Keywords:

type 2 diabetes,
aged

SUMMARY

With the increasing number of aged individuals in the population and the elevated prevalence of diabetes worldwide, there are more and older people with type 2 diabetes. Unfortunately, the management of diabetes in the elderly is not easy. Older people are heterogeneous. Hypoglycemia and hyperglycemia crises are more frequent and dangerous to older patients. Comorbidities, functional impairment and the available support system may influence the management of the disease. The target of glycemic control in the elderly should be based on individual conditions. Although the number of clinical trials relating to the management of type 2 diabetes in the elderly is limited, organizations have provided guidelines or statements about type 2 diabetes in the elderly. There are approved therapies or medicines for type 2 diabetes controls, but we should have more considerations for aged patients with type 2 diabetes.

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1. Introduction

By 2050, the proportion of older people in the population will increase from 15% to 25%.¹ The incidence of type 2 diabetes rises with aging. According to the Taiwan Nationwide Health Insurance database from 2000 to 2009², the diabetes prevalence rates were 21.97% for women aged 60–79 years and 23.97% for women aged 80 years and older. For men in the same age groups, the prevalence rates were 19.97% and 20.27%. The high prevalence of diabetes mellitus in the elderly challenges the medical systems.

There are some difficulties that arise from the management of type 2 diabetes in the elderly. First, it is hard to define the terms “elderly” or “older people.” The United Nations (UN) considers people 60 years of age or older to be part of the older population.³ The International Diabetes Federation (IDF) task force feels that a threshold of 70 or older ensures that people with diabetes will be more likely to exhibit those characteristics.¹ “Standards of Medical Care in Diabetes—2018” by the American Diabetes Association

(ADA) defined the aged as those > 65 years.⁴ The International Association of Gerontology and Geriatrics (IAGG) and the European Diabetes Working Party for Older People (EDWPOP) have a consensus statement for diabetes in older people, and it has limited our scope to those 70 years and older.⁵

Second, the different age thresholds can define geriatric age, but those could not match chronological and biological age in different continents. The heterogeneity of disease duration, the number and severity of complications and comorbidities, socioeconomic status, the degree of frailty and personal functions present in older people with diabetes all must be considered.⁶ The application of clinical guidelines to older patients should be based on the individual's specific conditions.¹

Many randomized controlled trials (RCTs) excluded elderly individuals to reduce the risks in performance. The IDF recognized that the evidence-based guidelines for older people with diabetes are based on deduced evidence from clinical studies in younger adults and they have limitations.¹

2. The considerations of diabetes care in the elderly

2.1. Hypoglycemia

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial with a mean age of 63 years tried to determine the effect of

[☆] The article is the review of the documents, including current practice guidelines, consensus statements and clinical trials which were published, so the ethical approval from IRB is not necessary.

* Corresponding author. Mackay Memorial Hospital, No. 92, Sec. 2, Zhongshan N. Rd., Taipei, 10449, Taiwan.

E-mail addresses: cerebrum22@gmail.com, drcwc@yahoo.com (W.-C. Chen).

intensive blood glucose control. However, it was terminated early due to the increased cardiovascular mortality of the intensive control arm.⁷ A severe hypoglycemic event was associated with cardiovascular death and all-cause mortality in the coming months in the Veterans Affairs Diabetes Trial.⁸

2.2. Geriatric syndrome, comorbidities and functional impairments

Geriatric syndromes are multifactorial health conditions and mean that the elderly have the accumulated effect of impairments in multiple systems and are therefore in a vulnerable situation. Diabetic complications and complicated medical conditions may contribute to cognitive decline. Type 2 diabetes was also associated with a 47% increased risk for all dementia, 39% for Alzheimer's dementia, and more than a 2-fold risk for vascular dementia among older adults in the community.⁹ More than 25% of aged patients with diabetes are victims of depression disorder.¹⁰ Depression impedes self-caring and adherence of diabetes management.¹¹ Diabetes mellitus increases the incidence of functional disability, and causes diabetic complications and complicated medical conditions. Those conditions increase the risks of diabetes management and decrease the quality of life.¹²

2.3. Hyperglycemia crisis

Hyperglycemic hyperosmolar state (HHS) and diabetic ketoacidosis (DKA) are considered hyperglycemic crises. Age is the risk factor of mortality.¹³ New diabetes cases in older individuals and older people with diabetes who are unaware of their disease or unable to take fluids are at risk for HHS.¹⁴

2.4. Polypharmacy

Polypharmacy is defined as the use of multiple medications. With the progression of diabetes, patients may need more medications and polypharmacy may present. Polypharmacy is also a factor in diabetes-related comorbidity. However, polypharmacy increases the risk of drug adverse effects, drug-drug interactions, drug-disease interactions and interference of medical adherence.^{15,16} Polypharmacy may mean that aged patients have more risk of falling.¹⁷

2.5. Support system

Due to possible frailty, cognitive decline, comorbidity and functional impairment, a support system is more important for older adults with diabetes than for younger adults.^{12,18}

2.6. The target of treatment

A multicenter, prospective RCT¹⁹ included 1173 older people in Japan (mean age was 72) with type 2 diabetes and followed them for 3 years. There was a small but significant difference in HbA1c between the intensive and conservative groups (7.9% vs 8.1%, $P < 0.05$) in the first year and not a significant difference in the next 2 years. There was no significant difference in fatal and non-fatal events. A retrospective cohort study with 71,092 patients with type 2 diabetes and who were ≥ 60 years of age in Northern California found that an A1C level $< 8\%$ in older people could reduce the complications and mortality, but an A1C level $< 6\%$ was related to mortality risk.²⁰ A U-shape relationship was found between A1C and mortality in the elderly with type 2 diabetes.

For most patients, the HbA1c target is suggested as below 7%^{1,21–23} or 6.5%²⁴ in current practice guidelines. Patient-centered management within those guidelines is suggested,^{22,23,25} with those options having a balance between the benefits of diabetes control and the risks of hypoglycemia.

The glycemic goals of the guides from those major organizations are from 7.0% to 8.5% (Table 1).

3. Options of medication

3.1. Metformin

In the guidelines or consensus statements of IAGG & EDWPOP, ADA & AGS and IDF, Metformin can be considered as the first-line medication. The outcome trials of metformin for older patients with diabetes are lacking, but a cohort study suggests that metformin reduces mortality and prevents frailty in older patients with diabetes.²⁸

Metformin has some limitations. Gastrointestinal upset is the most common adverse event in clinical practice. Fatal lactic acidosis is the major adverse event with the most concerns. Metformin is contraindicated in the condition of renal-function impairment, dehydration or chronic diseases with tissue hypoxia, etc. Other

Table 1

The glycemic targets from the clinical guides or consensus reports from the major organizations.

Organizations	Years	Glycemic goal of HbA1c for the elderly with diabetes
IAGG & EDWPOP ⁵	2012	7%–7.5%
ADA & AGS ¹⁵	2012	Healthy: $< 7.5\%$ Complex/intermediate: $< 8.0\%$ Very complex/poor health: $< 8.5\%$
IDF ¹	2013	Functionally independent: 7.0%–7.5% Functionally dependent: 7.0%–8.0% Frail: Up to 8.5% Dementia: Up to 8.5%
CDA ^{22,26}	2013	End of life: Avoid symptomatic hyperglycemia HbA1C target $\leq 8.5\%$ for patients with limited life expectancy, functional dependency, a history of severe hypoglycemia, advanced comorbidities, or a failure to target with treatment intensification The same glycemic targets apply to the healthy elderly as to younger people with diabetes.
JDS ²⁷	2013	1% higher for frail elderly patients than that for other age groups
ADA, "Older Adults: Standards of Medical Care in Diabetes-2018" ⁴	2018	Healthy status, HbA1c $< 7.5\%$ Complex/intermediate health, HbA1c $< 8\%$ Very complex/poor health, HbA1c $< 8.5\%$

CDA, Canadian Diabetes Association; JDS, Japan Diabetes Society.

Table 2
The advantages and disadvantages of glucose lowering therapies in older people with type 2 diabetes.

Categories	Advantages	Disadvantages	Contraindications	Special Considerations for the Elderly
Biguanide (Metformin)	<ul style="list-style-type: none"> • Efficacy • Low hypoglycemia risk • Low cost • Neutral to body weight • Benefits of cardiovascular outcome 	<ul style="list-style-type: none"> • GI intolerance • Lactic acidosis with poor perfusion status • Vitamin B12 deficiency 	<ul style="list-style-type: none"> • Renal dysfunction • CHF 	<ul style="list-style-type: none"> • Consider as the first-line therapy in guidelines or statements • Older people have more possibility of contraindications.
Sulfonylurea	<ul style="list-style-type: none"> • Efficacy • Low cost 	<ul style="list-style-type: none"> • Hypoglycemia • Body weight gain 		<ul style="list-style-type: none"> • Consider other OADs first for elderly patients with high risk of hypoglycemia • Start low dosage and titrate slowly • Dosing frequency effects compliance
Meglitinide (Glinides)	<ul style="list-style-type: none"> • Fast on, fast off • Less prolonged hypoglycemia • Effective in postprandial hyperglycemia 	<ul style="list-style-type: none"> • Greater dosing frequency • Weight gain • Relatively high cost 		<ul style="list-style-type: none"> • Dosing frequency effects compliance
DDP4-I	<ul style="list-style-type: none"> • Intermediate efficacy • Low hypoglycemia risk • Good tolerance • Neutral to body weight 	<ul style="list-style-type: none"> • High cost 	<ul style="list-style-type: none"> • Risk of pancreatitis 	<ul style="list-style-type: none"> • Increased risk of hospitalization for CHF?
TZD	<ul style="list-style-type: none"> • Efficacy • Low hypoglycemia risk • Benefits of lipid profiles • Possible secondary prevention for cardiovascular outcomes • Good durability 	<ul style="list-style-type: none"> • Edema • Body weight gain • Risk of CHF progression • High cost • Increased risk of long bone fracture in elderly females • Elevation of serum AST, ALT 	<ul style="list-style-type: none"> • CHF • Serum AST, ALT > 2.5 times of reference range 	<ul style="list-style-type: none"> • Risk of CHF • Females with osteoporosis?
A-glucosidase inhibitor	<ul style="list-style-type: none"> • Low hypoglycemia risk • Effective in postprandial hyperglycemia • Body weight loss 	<ul style="list-style-type: none"> • Abdominal illness, ex flatul, diarrhea • More dosing frequency • Body weight loss in the frail elderly 	<ul style="list-style-type: none"> • Renal dysfunction 	<ul style="list-style-type: none"> • Abdominal illness and dosing frequency effect compliance.
SGLT2 inhibitor	<ul style="list-style-type: none"> • Intermediate efficacy independent of insulin • Low hypoglycemia risk • Body weight decrease • Decreased SBP 	<ul style="list-style-type: none"> • Urinary tract infection • Genital infection • Fluid loss • High cost 	<ul style="list-style-type: none"> • Renal dysfunction 	<ul style="list-style-type: none"> • Frequent urination and genital infection effect compliance. • Body weight loss in the frail elderly is unfavorable • Older people have less renal function and it causes contraindication
G-1 analogue	<ul style="list-style-type: none"> • Effective • Low hypoglycemia risk • Body weight decrease 	<ul style="list-style-type: none"> • Likely abdominal illness, primarily nausea • Body weight loss in the frail elderly • Risk of pancreatitis • Subcutaneous injection • High cost 	<ul style="list-style-type: none"> • Acute pancreatitis 	<ul style="list-style-type: none"> • Body weight loss in the frail elderly • Cautious use in renal dysfunction
Insulin and insulin analogues	<ul style="list-style-type: none"> • Applications in all conditions 	<ul style="list-style-type: none"> • Risk of hypoglycemia • Weight gain • Injection • Insulin analogue cost high with high dosage 		<ul style="list-style-type: none"> • Require patients' ability or support from caregiver.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHF, congestive heart failure; GI, gastrointestinal.

usual adverse events from metformin include Vitamin B12 deficiency. It is notable that Vitamin B12 deficiency occurs frequently (>20%) among the elderly.²⁹

3.2. Sulfonylurea and meglitinides

Sulfonylureas (SUs) and meglitinides (glinides) are insulin secretagogues (ISs). With the rapid onset and short duration of action, glinides have lower risk for hypoglycemia than SUs but more dosing frequency and higher cost.¹⁵ Because of the high efficacy, the low cost and the availability,^{1,30} ISs are common in clinical practice. However, SUs have the disadvantages of leading to body weight gain and having a higher risk of hypoglycemia. SUs, which can be prescribed in patients to be taken with regular meals, can be used in the management of hypoglycemia¹; glinides can be used when people have irregular meal timing or dementia.^{1,15}

In the statement by IAGG and EWDDPOP,⁵ SUs should be avoided in patients with a higher risk of hypoglycemia. In the

consensus report of ADA and AGS,¹⁵ prescribing glyburide (glibenclamide) is not recommended in older people because of its high hypoglycemia risk; glinides are suggested in the case of irregular meal timing.

3.3. Dipeptidyl peptidase-4 Inhibitors

Dipeptidyl peptidase-4 inhibitors (DPP4-Is) are efficient, effective for postprandial hyperglycemia, well tolerated, neutral to body weight, and have less risk of hypoglycemia. However, their high cost may limit their use. Because DPP4-I has better tolerability and causes less hypoglycemia, the clinical trials of DPP4-I enrolled older people, and the post hoc analyses presented the efficacy and showed less hypoglycemia from the uses of DPP4-Is in the elderly.^{31,32} Compared to SU, DPP4i have protective effect on cognitive impairment in aged diabetic patients with mild cognitive impairment because of less glycemic variability and less risk of hypoglycemia.³³

3.4. Thiazolidinediones

Thiazolidinediones (TZDs) improve insulin sensitivity. These drugs are not associated with an increased risk of hypoglycemia and have good durability. Edema, body weight gain, congestive heart failure and the risk of fracture in female patients limit the applications in aged patients.

3.5. α -Glucosidase inhibitors

α -Glucosidase inhibitors (AGIs) are effective, especially in lowering postprandial hyperglycemia. There are beneficial effects on body weight and a low risk of hypoglycemia. The most adverse event is gastrointestinal upset. Frequent dosing may also limit the use in the elderly.¹⁵

3.6. Sodium-glucose co-transporter 2

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are a new class of OAD. They also have the effect of BW loss and a low risk of hypoglycemia. But the risks of genital infection, urinary tract infection, hypovolemia, postural hypotension and weight loss may limit their use in the elderly.¹ This new class of OADs may cost more than others. Renal dysfunction is also a contraindication. The EMPA-REG clinical outcome trial^{34,35} and the CANVAS clinical outcome trial³⁶ found that these inhibitors were safe and had a beneficial cardiovascular and renal outcome in patients with type 2 diabetes. The mean ages of the population in these two trials were about 63 years. The subgroup analysis of the EMPA-REG trial found that patients age ≥ 65 years had a better primary outcome and all-cause mortality.³⁴

3.7. Glucagon-like peptide-1 agonist

Glucagon-like peptide-1 (GLP-1) agonist has the benefits of postprandial hyperglycemia control, low risk of hypoglycemia and the effect of weight loss. The LEADER trial³⁷ and the SUSTAIN-6 trial³⁸ also found a cardiovascular benefit in patients with type 2 diabetes. Nausea is the most common adverse event. GLP-1 agonists should be used with subcutaneous injection and this would be the barrier for clinical application. Long-acting GLP-1 agonists can have less dosing frequency and help to conquer the clinical application barrier. The cost of GLP-1 agonists may limit clinical use.

3.8. Insulin

Insulin therapy for diabetes has efficacy but risk of hypoglycemia and anabolic effects including body weight gain. Subcutaneous injection is still necessary for clinical application. The ORING trial, a large RCT, found the neural effect on cardiovascular outcomes and cancer.³⁹ There are barriers to insulin therapy. Comorbidities, visual problems, impaired manual dexterity, poor functioning or cognition problems are barriers to some aged patients.⁴⁰ An RCT compared insulin glargine and premixed insulin lispro Mix75/25 in patients ≥ 65 years of age. It found that the premixed insulin lispro group had longer durability of glycemic control than the glargine group.⁴¹ However, a complicated insulin delivery protocol may increase the risk of hypoglycemia.⁴² All insulin therapy in older patients should be based on individual conditions.

3.9. Choices of medical therapy

Physicians choosing medicines for older patients should evaluate all patients' individual, related conditions and understand the characteristics of glucose-lowering agents (Table 2).

4. Conclusion

The heterogeneous characteristics of older patients make glycemic control neither simple nor easy. Some organizations provided guidelines or statements pertaining to type 2 diabetes management in older people, but only the IDF guidelines gave a comprehensive suggestion. The most important thing is to understand the considerations of diabetes care in older people and to have individualized management based on patients' individual conditions.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ijge.2018.05.008>.

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