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Optimizing Glycemic Control of Diabetes Mellitus in Older Adults – A Tailored Approach

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Abstract

The prevalence as well as the incidence of diabetes mellitus has been increasing worldwide. In an aging society, this disorder in older adults contributes to these increases. Older people are more vulnerable than younger people to developing excessive fat deposition and reduction in skeletal muscle because of a sedentary lifestyle, lower energy expenditure, and physical alterations due to aging, which can lead to the development of insulin resistance. The capacity of pancreatic beta cells to regenerate and differentiate is reduced in older people, which predisposes them to insulin deficiency. These two pathophysiological alterations underlie the development of glucose intolerance. With significantly longer life spans thanks to the advances in health care, it is imperative to attain optimal glycemic control in this specific population to prevent diabetes-related chronic complications. In addition to life style modifications such as dietary control and exercise for obese patients and those who could benefit from moderate weight loss, antidiabetic agents are frequently required to achieve prespecified treatment goals. Delivery of these medications in an efficient and safe manner must be tailored to individual requirements to maintain an intricate balance between reasonable glycemic control and hypoglycemia. Older adults with diabetes are vulnerable to hypoglycemia due to a long history of the disease and frailty from aging. As long as factors that impact the pharmacokinetics and pharmacodynamics of these agents are considered, such as renal function and adherence to polypharmacy, oral agents are more welcomed by older people because of convenience of administration and proved clinical efficacy. When oral agents fail, insulin therapy may be unavoidable when trying to pursue an optimal glycemic target. (J Intern Med Taiwan 2019; 30: 132-149)

Key Words: Diabetes mellitus, Glycemic control, Older adult

The scope of diabetes mellitus in the older adults

As people age, they may have more chronic diseases than their younger counterparts. The incidence of diabetes is increasing with the increase in the geriatric population[1,2]. Taiwan's Ministry of the Interior reported that Taiwan has officially entered the stage of an "aged society" as Taiwanese people over 65 years old accounted for 14.05% of the country's total population at the end of March, 2018. In 2017, the International Diabetes Federation estimated that 122.8 million people worldwide between 65 and 99 years old had diabetes, with a prevalence

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of 18.8%[3]. The increasing prevalence of diabetes in older adults is not only due to deteriorating pancreatic beta cell function and insulin sensitivity from increased adiposity and reduced skeletal muscle mass in the process of aging, but also the occurrence of this disease at an earlier age than previously. Geriatric adults have a longer life expectancy thanks to improved health care policies and quality nowadays. Physicians must provide optimal management of this disease in the expanding geriatric population[4,5].

Pathophysiology of type 2 diabetes mellitus in older adults

The pathophysiology of type 2 diabetes mellitus (T2DM) in older adults is not much different from that in their younger counterparts, but the severity might be exaggerated through the combined effects of deteriorating pancreatic beta cell function and the insulin effect as people age. Many studies have reported that the turnover, regeneration, and proliferation of pancreatic beta cells are impaired in the process of aging[6-17]. The replication refractory period and the time between cell divisions (G0 stage of the cell cycle) appear to lengthen with age[18]. In a study using the frequently sampled intravenous glucose tolerance test in normal-weight study subjects with comparable baseline glucose levels and fat mass, older men had a 50% loss of beta cell function compared with the younger group[19].

Impaired insulin function (insulin resistance) at various tissue levels in the elderly could be exaggerated by decreased physical activity and abnormal adipose tissue deposition with a simultaneous loss of skeletal muscle mass. This is called sarcopenic obesity, a relatively newly-defined clinical entity gaining widespread attention as having significant impact in geriatric healthcare. The chronological age per se may have no independent influence on the development of insulin resistance when adiposity is considered in the analysis. Visceral adiposity, a notable major factor causing insulin insensitivity, together with reduced beta cell function, results in the development of glucose intolerance[20-26].

The life style of older adults also contributes to the development of decreased insulin sensitivity. Reduced energy expenditure as they become more sedentary, and lack of access to proper exercise facilities may result in excessive accumulation of adipose tissue, especially visceral fat, with a concomitant reduction in lean muscle mass, mainly in the skeletal musculature which is the major site of glucose disposal[27-31]. A study investigating the relationship between skeletal muscle mass (using dual-energy X-ray absorptiometry) and various components of metabolic syndrome in different age groups in Korea, found that, sarcopenia was an early predictor for the development of diabetes and metabolic syndrome, particularly in the elderly, even in the absence of obesity[32]. Although a sedentary life in older adults may increase body adiposity, studies showed that increased physical activity significantly improved insulin sensitivity, decreased the incidence of diabetes, and improved glycemic control in the elderly with diabetes[33,34]. Exercise benefits insulin sensitivity at the molecular level. Mitochondrial function in terms of adenosine triphosphate (ATP) production is reduced in the older population compared with their younger counterparts, and exercise reverses the age-related decline in oxidative capacity and ATP production. These findings support the evidence of enhanced insulin sensitivity after exercise training[35].

The goal of glycemic control in older adults with diabetes

although many older adults with diabetes are robust enough to lead an independent life, a significant number are frail generally and have comorbidities such as impaired vision, reduced muscle mass, reduced bone density, and diabetic neuropathy (sensory, motor or autonomic), which may independently

or in clusters lead to inability to maintain homeostasis, especially in the presence of acute stress. When there is accompanying impaired renal function or an impaired counter-regulatory response to hypoglycemia after a long history of diabetes, the risk of hypoglycemia-associated complications increases[36-42]. Although some investigators found that a higher glycated hemoglobin (HBA1c) level was associated with walking difficulty, low physical performance, increased incident frailty, and lower extremity mobility limitations in women between 70 and 79 years old[43], there is controversy concerning the impact of hyperglycemia on the general performance of older adults. In another study, higher blood glucose was associated with increased incident frailty in nondiabetic elderly people. However, in elderly people with diabetes, a U-shaped phenomenon was noted, with blood glucose levels higher than 180 mg/dL and lower than 160 mg/dL both linked to higher incident frailty. The causality underlying this phenomenon requires more research[44]. In a recent study using the Clinical Frailty Scale in elderly diabetes patients in Japan, more severe frailty was associated with advancing age, low levels of HbA1c, serum albumin, total cholesterol, and high-density lipoprotein cholesterol, and low systolic blood pressure, as well as low body weight, suggesting a role of reverse metabolism owing to malnutrition as a cause of frailty[45]. With increasing recognition that hypoglycemia is a major drawback in intensive glycemic control, many academic societies have modified targets to less stringent levels tailored to the general performance of this special group of patients. The current guidelines of the academic society of Taiwan for glycemic control in older adults with diabetes are no exception[46]. Older adults who are functionally and cognitively intact and have a significant life expectancy should receive diabetes care using goals developed for younger adults. The goals may be relaxed for older adults not meeting the above criteria (Table 1)[46,47]. But, hyperglycemia leading to symptoms or risk of acute hyperglycemic complications should be avoided in all patients[48-53].

Starting with non-Pharmacological management of diabetes in older adults

When diabetes is diagnosed or already exists

Table 1. A framework for treatment goals for glycemia in older adults with diabetes (adapted from 46, 47)

Patient characteristics/health status	Rationale	Reasonable A1C goal‡	Fasting or pre-prandial glucose	Bedtime glucose
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	< 7.5%	90 – 130 mg/dL	90 – 150 mg/dL
Complex/intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	< 8.0%	90 – 150 mg/dL	100 – 180 mg/dL
Very complex/poor health (end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefits uncertain	< 8.5%†	100 – 180 mg/dL	110 – 200 mg/dL

ADL, activities of daily living. ‡A lower A1C goal may be set if achievable without recurrent or severe hypoglycemia or undue treatment burden. *Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. The term“multiple” means at least 3, but many patients may have 5 or more. **The presence of a single end-stage chronic illness, such as stage 3 - 4 congestive heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy. †A1C of 8.5% equates to an estimated average glucose of ~200 mg/dL. Looser A1C targets above 8.5% are not recommended as they may expose patients to more frequent high glucose values and acute risks from glycosuria, dehydration, hyperglycemic hyperosmolar syndrome, and poor wound healing.

in an older adult, the impact of geriatric syndrome on the management of diabetes has to be considered when planning treatment. This syndrome has multiple facets manifesting as functional disabilities in vision and hearing, falls, depression, cognitive impairment, and malnutrition. These disabilities can not only can lead to frailty with loss of independence in daily living and a low quality of life, but may also become major obstacles in the treatment and care of patients with diabetes. A thorough medical history is needed to identify any coexisting diabetes-related complications or comorbidities. Even in newly diagnosed patients, the establishment of diabetes almost always has gone through a long journey during which certain cardiovascular risk factors could have already developed and which could raise the risk of cardiovascular events if unnoticed and untreated[54-57]. Efficient and holistic care management requires a well-organized team of physicians, nurse practitioners, nurses, diabetes educators, dietitians, pharmacists, social workers, and mental health professionals. The involvement of both the patient and family in an active treatment strategy is also highly recommended. Self-monitoring of blood glucose, for example, can alert the patient and caregivers to glycemic excursions or swings, and can provide physicians with useful information needed to adjust treatment[58-61].

As a rule, lifestyle modification including regular physical exercise with mild-to-moderate loss of body weight in obese patients should be commenced before or at the same time as pharmacological therapy. Nutritional counseling and exercise training resulting in a loss of body weight in candidate patients has been found to not only improve insulin sensitivity but also beta cell function. Both aerobic exercise and whole-body resistance training are feasible options in older adults to increase skeletal muscle mass and decrease fat deposition, with improvement in insulin sensitivity and better glycemic control[33,62-70]. There is some concern about body weight loss in the elderly[71]. Researchers have found that when intentional weight loss is achieved by a combination of planned caloric calculation and regular aerobic exercise such as resistance training, the loss of skeletal muscle mass is minimal and is accompanied by increases in physical function and bone density[72-74].

Flexibility training and balance training are recommended 2-3 times/week for older adults with diabetes. The American Diabetes Association recommends yoga and tai chi, based on individual preference, to increase flexibility, muscular strength, and balance[47]. The exercises should be designed to avoid harm to the feet and joints of geriatric people, who are more vulnerable to injury than younger people. Walking barefoot on a pebble route is absolutely contraindicated for older patients since the proprioceptive or pressure sensation may be impaired, especially in those with a long history of diabetes with a high risk of diabetic neuropathy[59,75,76].

Pharmacological management of diabetes in older adults

Oral antidiabetic agents (OADs) are still the most commonly prescribed agents in diabetic patients regardless of age. Unless specific clinical conditions such as acute illness or a catabolism from severe hyperglycemia require the use of insulin therapy, oral agents warrant appraisal in older adults because of their convenience in administration and proved efficacy in glycemic control, with concern about safety issues[77-80]. The characteristics of currently approved medications for T2DM are summarized in Table 2.

Biguanides

Biguanides have long been the first line of OADs considered due to their efficacy in lowering glucose and safety profile. Contraindications include significantly impaired renal or liver function, heart failure, or previous difficulty with these medica-

Table 2. Antidiabetic agents used in older adults with type 2 diabetes

Medication class/ mechanism of action	HBA1c reduced	Advantages	Disadvantages	Caveats in the older population
Biguanides/Decrease hepatic glucose production, increase GLP-1 secretion.	~ 1%	• Negligible risk of hypoglycemia as monotherapy • Low cost • Well understood side effects	• Bloating, diarrhea • B12 deficiency • Lactic acidosis (rare)	• Initiate at low dose, increase dose slowly and take with food to decrease gas, diarrhea • May cause weight loss in frail older adults • Measure liver function, serum creatinine and eGFR initially, then periodically and with any increase in dose • Avoid initiating and stop use if eGFR < 30 • Contraindicated in: advanced liver disease, alcohol excess, decompensated CHF, acute intercurrent illness, dehydration. • Withhold use when receiving radiography containing contrast medium.
Insulin secretagogues (Sulfonylureas/Meglinides)/Stimulate β cell insulin secretion	0.7-1.3%	• Fast and high efficacy • Low cost	• High risk of hypoglycemia • Body weight gain	• Consider use of short acting sulfonylureas or meglinides with renal disease to reduce the risk of hypoglycemia • Repaglinide or nateglinide may be useful for those with postprandial hyperglycemia or with hypoglycemia on sulfonylureas • Watch for increased risk of hypoglycemia with impaired renal function, acute illness, hospitalization, weight loss, lack of appetite, skipped meals and those with memory issues
Thiazolidinediones (TZDs)/ Improve glucose transport, and decrease hepatic glucose production	0.8-0.9%	• No risk of hypoglycemia as monotherapy • Can be used in renal impairment but may increase fluid retention	• Body weight gain • Fluid retention with peripheral edema • CHF progression • Increases bone loss and risk for bone fracture	• Avoid use in patients with Class III and Class IV CHF
Alpha-glucosidase Inhibitors/ Delay absorption and breakdown of carbohydrates in small intestine	0.7-0.8%	• Low risk of hypoglycemia as monotherapy • Good efficacy when postprandial hyperglycemia predominates	• Bloating, flatulence, diarrhea	• Use pure glucose to treat hypoglycemia as the drugs decrease absorption of other forms of carbohydrate • Contraindicated in chronic intestinal disorders • Do not use in renal impairment (creatinine > 2.0 mg/dL) • Initiate at low dose and increase slowly to decrease flatulence
DPP4 inhibitors/ Slow the inactivation of incretin hormones, stimulate insulin and suppress glucagon secretion	0.5-0.7%	• Lower risk of hypoglycemia when used as monotherapy • Controlling post prandial glucose elevations	• Occasional diarrhea and stomach discomfort. • High cost	• Reduce dose of insulin secretagogues or insulin in combination therapy to lower risk of hypoglycemia • Stop medication if pancreatitis is suspected when a DPP-4 inhibitor is in use • Increased risk of hospitalization for CHF (?)
Incretin mimetics as GLP1-RA/ Directly raise GLP-1 levels to stimulate insulin and suppress glucagon secretion, enhance satiety	1.0%	• Low risk of hypoglycemia as monotherapy • Weight reduction	• Nausea, diarrhea • Increased risk of pancreatitis • Require subcutaneous injection • High cost	• Reduce dose of insulin secretagogues or insulin in combination therapy to lower risk of hypoglycemia • Enhanced satiety may affect nutritional status in frail older adults • Cautious use in renal dysfunction • Contraindicated in acute pancreatitis

(continued)

Table 2. Antidiabetic agents used in older adults with type 2 diabetes (continued)

Medication class/ mechanism of action	HBA1c reduced	Advantages	Disadvantages	Caveats in the older population
Sodium-Glucose Co-Transporter Inhibitors (SGLT2i)/ Enhance urinary excretion of glucose by blocking reabsorption of glucose from the proximal tubule of the kidney	0.4-0.7%	• Low risk of hypoglycemia as monotherapy • Weight reduction	• Increased risk of genital mycotic infections and UTI (especially in females)	• Risk of euglycemic ketoacidosis • May reduce blood pressure when not desired (especially with concomitant use of diuretics or in dehydration) • May result in dehydration, hyperkalemia • May result in weight loss in frail older adults • Dose adjustment required in renal function impairment: ▪ Empagliflozine: dose reduction when eGFR < 60, avoid use when < 45 ▪ Dapagliflozine: Avoid use when eGFR < 60 ▪ Canagliflozine: dose reduction when eGFR < 60, avoid use when < 45
Insulin therapy	0.9-1.2% or more	• Improve glycemic control as monotherapy or as adjunct when other anti-diabetic agents fail	• High risk of hypoglycemia • Difficulties in self-administration for older adults	• Long acting insulin can be started as simple and safe regimen along with other non-insulin anti-diabetic agents to control postprandial hyperglycemia • Consider the individual's cognitive abilities, dexterity and visual acuity before considering the use of insulin. • Reduce dose to avoid hypoglycemia when renal function is impaired

Abbreviations: CHF: congestive heart failure.

tions in patients, mainly from gastrointestinal irritation. The United Kingdom Prospective Diabetes Study found that patients taking metformin had significantly lower rates of myocardial infarction and related mortality than patients taking sulfonylureas (SUs) or insulin therapy[81]. A survey from a healthcare database in Canada investigated mortality in new users of oral antidiabetic agents over 5 years. The mortality rates in patients on metformin monotherapy (13.8%) or in combination with SUs (13.6%) were significantly lower than those on SU monotherapy (24.7%)[82]. A retrospective study in China analyzed 3400 pairs of diabetic patients who were started on metformin and lifestyle modification or life style modification alone. Over 5 years, those on metformin therapy had significant risk reductions in all-cause mortality by 29.5% and cardiovascular events by 30-35% (except heart failure)[83]. However, a review article on the impact of metformin on cardiovascular disease derived from a meta-analysis of randomized trials reported uncertainty regarding its benefit in reducing cardiovascular risks when used as a first line OAD[84]. Furthermore, with the advent of novel antidiabetic agents, the role of metformin as a first line oral antidiabetic agent has been challenged in the past several years, as consistent findings of significant heart protection from newer agents have been reported in long-term, prospective, randomized control trials. The use of the sodium-glucose co-transporter subtype 2 inhibitor (SGLT2i) empagliflozine was found to result in profound reduction in all-cause mortality and cardiovascular mortality, as well as hospitalization from heart failure in the EMPA-REG trial in diabetic patients with high risks of cardiovascular events[85]. The administration of the glucagon-like peptide-1 receptor agonist (GLP-1RA) liraglutide was also found to significantly reduce the cardiovascular risk com-

pared with a placebo[86]. Various academic societies have endorsed the use of these newer antidiabetic agents as second line medications added to metformin in diabetic patients who are at risk of or already have cardiovascular disorders (e.g. heart failure, existing coronary heart disease, or recent acute coronary syndrome), because of solid evidence of cardioprotection compared with other agents[47,52,87,88].

The dosage of metformin must be adjusted according to renal function as estimated by the glomerular filtration rate (GFR) (eGFR, mL/min/1.73 m^2) derived from serum creatinine levels. In a study in 451 diabetic patients, a dosage-response curve was noted with a range between 500 mg and 2000 mg daily. A further titration up to 2500 mg daily did not result in further significant benefit in glycemic control[89]. A recent study in Japanese diabetic patients 21 to 84 years old (mean age of 64) with a mean eGFR of 78.3 ± 19.5 mL/min/1.73 m^2 suggested that the efficacy of metformin is dose-related and a daily dose of 1500 mg had a significant glucose-lowering effect. A further titration up to 2250 mg daily, the maximum dose used in that study protocol, had a trend toward further improvement in the glycemic profile. Dosing frequencies of two and three times per day in patients taking 1500 mg/day resulted in similar efficacy. Most side effects were in the gastrointestinal system[90]. Inconsistencies in the recommended highest dosages in different studies could be caused by individual responsiveness to metformin when given as a monotherapy. Diabetes treatment is rarely limited to the use of a single agent and combination therapy is almost always used because of the multiple pathophysiological processes underlying diabetes development and progression. As with other OADs, the selection of the proper dosage and frequency and timing of metformin administration largely depends on the characteristics of co-administered agents[91].

One risk of metformin is buildup of lactic acid with poor renal function. The United States Food and Drug Administration (USFDA) advises that metformin not be used when the eGFR is < 30 mL/min/1.73 m^2 [92]. Although the eGFR declines as people age, age per se may not be a factor contributing to the accumulation of lactic acid with metformin use. Renal function is the dominant clinical factor of concern when metformin is considered, regardless of age[93].

Sulfonylureas and metiglinides as insulin secretagogues

The second most commonly prescribed OADs in most regions and countries are the sulfolnylureas (SUs). As the earliest one among the various classes of OADs in the drug development history, SUs have always been one of the most-widely prescribed till nowadays, although there have been voices and noises arising several years ago debating on its role in the management of diabetes out of the following observations and concerns: 1. possible links between its use and increased risk of cardiovascular as well as all-cause mortalities, and 2. the debut of other new antidiabetic agents that have lower risk in causing severe hypoglycemia with an appreciable antidiabetic efficacy at the same time, as well as significant benefits in cardio- and renal protection[94-100]. Nevertheless, when used judiciously, SUs are high efficacy antidiabetic agents which can bring glycemic control to a prespecified target in a shorter time compared with other oral therapies[101,102]. Among longer duration SUs, gliclazide is less likely to cause hypoglycemia than glyburide and glimepiride[103].

Meglitinides, a class of non-sulfonylurea insulin secretagogues, effectively lower the postprandial glucose level to achieve smooth glycemic excursion after a meal. They carry a lower risk of hypoglycemia due to their fast-on and fast-off pharmacokinetics in insulin stimulation, an advantage especially beneficial for older adults. With a rapid onset of action after administration before or with a meal, meglitinides are flexible and feasible for patients

who have irregular meals. For a given dose of repaglinide, inactive metabolites are mainly excreted via the bile (~90%). Only 8% is excreted in the urine and less than 2% of the parent drug is recovered in the feces[104-107]. In diabetic patients with chronic kidney disease of stage 2-3, repaglinide has the same pharmacokinetic characteristics as seen in diabetics with normal renal function and thus carries a lower risk of hypoglycemia risk than long-acting SUs[108].

Thiazolidinediones as insulin sensitizers

Thiazolidinediones (TZD) improve insulin sensitivity by acting as ligands for the activation of the nuclear peroxisome proliferator-activated receptor gamma in adipocytes. In an earlier study on the mechanisms underlying the insulin-sensitizing effect of pioglitazone, it was demonstrated that a shift in fat distribution from visceral to subcutaneous areas is associated with improvements in hepatic and peripheral tissue sensitivity to insulin[109]. In a more recent study using ^{18}F-fluorodeoxyglucose-positron emission tomography and computed tomography, pioglitazone was found to significantly decrease the visceral fat volume and its metabolic activity in patients with impaired glucose tolerance or T2DM[110]. As visceral fat accumulation has been linked to a higher risk of cardiovascular diseases, the redistribution of visceral fat to subcutaneous sites with the use of TZD has been proposed to be protective for the cardiovascular system[111]. There are debates over the pros and cons of the role of different TZDs in heart protection. These agents are contraindicated in patients with evident heart failure or with ischemic heart disease who are vulnerable to the development of heart failure from fluid accumulation, a common side effect of TZDs[112-117]. The prudent use of TZDs has been proved effective for glycemic control, along with an improved lipid profile such as elevation of high-density lipoprotein cholesterol and lowering of triglycerides, theoretically beneficial to the cardiovascular system in diabetes patients with insulin resistance and metabolic syndrome[118].

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors lower plasma glucose by inhibiting the breakdown of complex carbohydrate at the small intestinal level with reduced absorption of simple sugar into the blood stream. In a study carried out in elderly patients with diabetes, acarbose was found to effectively lower HBA1c levels with improvement in both the fasting and incremental postprandial glucose values. Although the pharmacology of these agents does not involve insulin stimulation, with lowering of plasma glucose and the consequent amelioration of glucotoxicity, insulin sensitivity as assessed by the homeostasis model of assessment or insulin clamp method improved in clinical studies[119-122]. The side effects are mostly gastrointestinal with bloating, flatulence or abdominal distension from gas formation in the large intestine, symptoms that are tolerable for most patients, including the geriatric population[120].

Incretin therapy

Incretins, the peptides secreted from the gastrointestinal tract in response to various nutrients ingested into the alimentary tract, carbohydrates in particular, have been applied to clinical use in the past decade with success. Among the various incretins, glucagon-like peptide-1 (GLP-1) is the most widely investigated and appreciated in glycemic control strategies. When secreted from the L-cells located at the distal end of the ileum, GLP-1 is rapidly degraded by the dipeptidyl peptidase-4 (DPP4) from nearby intestinal epithelial cells within a few minutes so only 25% of the secreted amount reaches the portal circulation. A further 40-50% is destroyed in the liver and thus only 10-15% of the originally secreted amount enters the systemic circulation and may reach the pancreas to exert an insuli-

notropic effect (incretin effect). When the activity of DPP4 is inhibited by its antagonist (DPP4 inhibitor = DPP4i), the amount of GLP-1 that reaches the portal or peripheral circulation is enhanced with a consequent increase in the amount of insulin secreted from pancreatic beta cells. GLP-1 not only stimulates secretion of insulin but also suppresses glucagon secretion from the neighboring alpha cells. Through this synergistic effect, the circulatory glucose level is effectively lowered when plasma glucose is driven into insulin-sensitive peripheral tissues (muscle, liver, and adipose tissue) and when endogenous glucose production is reduced (gluconeogenesis from muscle and glycolysis from liver) due to the suppressed glucagon effect[123,124]. Beta cell dysfunction plays a more dominant role in the pathophysiology underlying T2DM than adiposity and insulin resistance in Asian patients compared with the Caucasian population, and incretin-based therapy has been proposed to have a more prominent role in the management of diabetes in East Asian people[125,126]. The low risk of hypoglycemia when used as monotherapy or when added to metformin merits its use in older adults with diabetes. With the exception of linagliptin, which is eliminated through the hepatic pathway, the dosages of DPP4i must be adjusted to renal function[127,128]. DPP4i can be used as monotherapy or in combination with any other oral antidiabetic agents or insulin therapy, but physicians should be cautious when prescribing concomitant SUs as the risk of hypoglycemia is significantly raised. The dose of SUs should be reduced or halved in this regimen[129]. The low risk of hypoglycemia in incretin therapy is derived from the lowering of the intracellular ATP/adenosine diphosphate (ATP/ADP) ratio during the glycolysis pathway in the beta cells when the ambient plasma blood glucose and hence the intra-cellular glucose level is accordingly low. Physiologically, a low ATP/ADP ratio would lead to the opening of the ATP-sensitive potassium (kATP) channels located on the cell membrane with consequent suppression of insulin secretion from beta cells, preventing a further lowering of blood glucose. However, when SUs are in use, these insulin secretagogues stimulate insulin secretion via high affinity with the sulfonylurea receptor-1 on the cell membrane even when the plasma glucose level is low, a coupling leading to the stimulation of insulin secretion through closing of the nearby kATP channels. Hypoglycemia ensues because of unchecked insulin secretion in the presence of SUs. At the same time, the high insulin levels incurred by SU action may suppress glucagon secretion, with loss of the protective role of this counter-regulatory hormone against hypoglycemia[130]. In a meta-analysis on the concomitant use of DPP4-i and SUs compared with SUs alone, the hypoglycemia risk was increased by 50% in the combination group with one excess case in every 17 cases thus treated[131]. In a Swedish nationwide study on the impact of SUs combined with metformin versus DPP4i combined with metformin, investigators found significantly higher risks of developing hypoglycemia, fatal and non-fatal cardiovascular diseases, and all-cause mortality in the SU-combination group. Univariate analyses showed increasing age and frailty were both risk factors, among others, in developing hypoglycemia and other parameters of interest[132]. The SU that carried the highest risk of hypoglycemia was glibenclamide. It has a long half-life and the metabolites still exert a secretagogue effect, especially when the plasma concentration builds up in patients with impaired renal function[133]. A higher risk of hypoglycemia was also noted when insulin as second line therapy was added to metformin, compared with adding DPP4i[134]. Thus, strong evidence shows that DPP4i carry a significantly lower risk of hypoglycemia when used alone or in combination with other antidiabetic agents, excluding SUs and insulin therapy, in the elderly diabetic population. This group is prone to hypoglycemia caused by inadequate nutrition, frailty from other comorbidi-

ties, or overtreatment medically[135].

GLP-1RAs administered by injection have gained a significant role in the management of diabetes since their debut in 2005. They not only have proved efficacious in lowering glucose, but also offer significant cardiovascular protection, with evidence obtained from randomized, placebo-controlled cardiovascular outcome trials[136]. In the LEADER trial, liraglutide significantly reduced the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke compared with a placebo in type 2 diabetes patients 50 years old or older with a history of coronary heart disease, cerebrovascular disease, peripheral vascular disease, or chronic kidney disease, and those 60 years old or older with at least one cardiovascular (CV) risk factor[137]. A meta-analysis of completed and ongoing clinical trials concluded that the CV benefits of the GLP-1RA regimens showed a class effect[138].

These novel findings on the benefits of antidiabetic agents, together with those addressed in the next section on sodium-glucose co-transporter subtype 2 (SGLT2) inhibitors, have gradually lead to a paradigm shift in the management of diabetes beyond glycemic control as the primary and only goal toward cardiovascular and renal protection.[139-141].

Sodium-glucose co-transporter inhibitors

SGLT2 inhibitors (SGLT2i) are novel OADs that lower glucose by promoting excessive glycosuria via inhibition of tubular reabsorption of filtered plasma glucose through the glomerulus. This working mechanism does not involve insulin secretion but may cause physiologically adaptive processes after glucose is drained from the body. This reduced plasma glucose concentration after excessive glycosuria is followed by reduced insulin secretion as well as enhanced glucagon secretion with a net increase in endogenous glucose production via gluconeogenesis, and formation of ketone bodies from metabolism of free fatty acids derived from the effect of glucagon on fat metabolism. An advantage when initiating these antidiabetic agents is significant reduction of body weight. This is welcomed by overweight and obese diabetic patients who may also obtain better glycemic control from reduction of fatty tissue, especially visceral fat, associated with improvement in insulin sensitivity[142-144].

SGLT2i can be used as monotherapy or in combination with any other antidiabetic agents, inclusive of insulin therapy[145]. In addition to the expected glucose lowering effect, the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial, one of the first large scale randomized, placebo-controlled clinical trials of its kind, found that empagliflozine could significantly reduce the risk of heart failure and related mortality[146]. The multiple nonglycemic effects of this new group of antidiabetic agents have been explored in an attempt to explain the mechanisms underlying these unexpected cardiovascular benefits. Plausible multifaceted experimental findings have been proposed, which include reductions in body weight, adipose tissue (visceral adiposity predominantly), and blood pressure (diuretic hypothesis), improvement in arterial stiffness, and less hyperinsulinemia[147]. An increase in ketone body formation which spares the failing heart from excessive oxygen consumption during synthesis of ATP, proposed as the “theory of thrifty substrate”, has also been theorized as the cause of the significant cardiovascular protection.[148]. The cardioprotective benefits of SGLT2i have been generally endorsed by clinical research outcomes and meta-analyses from multiple relevant studies[149,150].

SGLT2i lower plasma glucose by eliminating glucose into the urine, and adequate renal function is critical for the clinical effect. When renal function is impaired, the amount of glucose filtered

through the glomerulus is also reduced, followed by weakened glycemic control. Generally, these agents are contraindicated when the eGFR is lower than 30 ml/min/1.73 m^2 because of insignificant lowering of glucose and possible dehydration instead. The USFDA advises that physicians evaluate risk factors for kidney injury before starting these agents (including reduced blood volume, chronic kidney insufficiency, heart failure, and concomitant medications such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and non-steroidal anti-inflammatory drugs), follow up renal function periodically. The drugs should be discontinued promptly whenever there is evidence of acute kidney injury[151].

The significant glucosuric effect with the use of these agents may cause local irritation of the urethral mucosa or even urinary tract or genital infection. Risk factors for development of fungal genital infection include female gender and a previous history of fungal genital infections[152]. Clinical studies have shown that most infections are mycotic and antibiotics are effective as standard therapy. The antidiabetic regimen rarely needs to be stopped[153]. Hypovolemia can occur due to the diuretic effect. Patients taking diuretics for any other clinical reason should be observed to avoid impaired renal hemodynamics, hypotension, or orthostatic hypotension[154].

The use of SGLT2i in older adults has generally been deemed safe when the risks of hypoglycemia, volume depletion-related events, genital/urinary tract infection, polyuria, and increment in ketone body formation are considered before and during follow-up and when used judiciously[155-157].

Insulin therapy

If patients can accept the use of injections, and there are no contraindications to its use, insulin is generally considered to have the best treatment outcomes in terms of glycemic control for patients of all ages, as long as the dosage and frequency of administration are well designed and tailored to individual requirements. Insulin injections can be administered as initial therapy, especially in patients with extremely high plasma glucose levels (e.g. when HBA1c is > 9%) and other signs of a catabolic state from extreme hyperglycemia, or as add-on or combination therapy whenever more than one OAD does not give reasonable glycemic control. Insulin therapy consists of multiple modalities of administration, including basal, basal plus (one basal + one or two short-acting insulin injections administered before the larger meal(s) in a day), basal-bolus (one basal + short-acting insulin injection administered before each main meal), or mixed insulin with various formulae (e.g. 30/70, 25/75, or 50/50 as the short-acting/intermediate-acting ratio in the mixture). The regimen is tailored to each patient's clinical characteristics including the required frequency of administration, the injection devices available, dexterity of the individuals in handling injections, and family support for those who are dependent in daily activities. Conclusions from randomized, controlled clinical trials show better glycemic control with more frequent and complex insulin regimens compared with simpler regimens[158-160]. However, complex regimens may not be feasible for elderly people with physical or mental dysfunction. Therefore, for reasons of convenience and better adherence to therapy, long-acting insulin is usually started first with the aim of obtaining an acceptable fasting glucose level and a narrowing of the postprandial glucose excursion, when other factors such as dietary control and exercise intensity are maintained. Chien et al.[161] conducted a prospective study of the effects and complications of starting a basal insulin regimen in elderly (72.5 ± 5.3 year-old) and younger (52.6 ± 8.1 year-old) diabetic patients who had failed OAD therapy. After 24 weeks of treatment with insulin glargine, there were similar reductions in fasting blood glucose and HBA1c in both groups (81.3 ± 79.9 mg/dL vs 93.0 ±

82.5 mg/dL; 1.18 ± 1.76% % vs 1.49 ± 2.12% in the elderly and the younger groups, respectively, with $p > 0.5$ for intergroup comparison in both parameters). The incidence of hypoglycemia was low in both groups without statistical significance (9.4% vs 15.0%, elderly vs young, $p = 0.4733$ for intergroup comparison). This study indicates that basal insulin therapy (starting with 0.24 ± 0.11 U/kg in the elderly group) with gradual titration of dose according to careful clinical evaluation is safe in older adults with diabetes who do not achieve adequate glycemic control with two or more OADs. When the goal of fasting glucose has been reached but there is inadequate glycemic control as evidenced by high HBA1c or postprandial glucose profiles, a switch to a more complex regimen may be needed to avoid the annoying symptoms of chronic hyperglycemia, such as body weight loss, thirst, polyuria, nocturia, postural hypotension due to dehydration, and a decreased immune response. A study of Japanese diabetic patients who failed SU therapy found similar reductions of HBA1c from similar beginning levels (~ 9%) of -14.7~ -17.8% in patients with complex basal-bolus regimens and simpler pre-mixed regimens. Despite the absence of statistical significance, the absolute HBA1c levels reached were numerically lower in the basal-bolus group (6.9(6.2~7.3)% than the pre-mixed group (7.4(6.9~8.7)%)[162].

Conclusions

As the number of older adults with diabetes increases, healthcare professionals face more challenges in its management in this group of patients. A multi-disciplinary team is needed to deliver proficient and competent care using judicious prescription and evaluation of the advantages and disadvantages of various antidiabetic regimens. The goal is not only to achieve adequate glycemic control but also to prevent and minimize diabetes-related complications and comorbidities to lengthen the healthy life span of elderly patients living with diabetes.

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應用量身訂造的處置方式達到適當調控年長糖尿病患血糖值的目標

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摘　要

台灣的社會人口結構已經在2018年的3月底邁入高齡社會，定義是65歲以上的人口比例已超過總人口數的14%。隨著人類壽命增長及高齡化的現象，慢性疾病的盛行率亦明顯上升，糖尿病亦不例外。根據最新的國際糖尿病組織(IDF)的統計數字，全球高齡者的糖尿病盛行率已達18.8%，且預期會持續升高。年長者罹患糖尿病的病生理機制仍因胰臟β細胞製造及分泌胰島素功能不足，及周邊組織器官之胰島素阻抗現象引起，但與較年輕族群比較，因為運動量減少及基礎熱量消耗量下降，導致臟器脂肪更易堆積，但是骨骼肌量反而減少，使血糖代謝異常的程度加劇，引致糖尿病產生。因平均餘命延長，在年長者仍應積極調控血糖以期減少高血糖可能引起之併發症，如腎病變、視網膜病變、神經病變，或感染症，以維持或改善年長者的生活品質。調控血糖的治療策略仍應以生活模式的調整為出發點，尤其在肥胖者，適當的飲食控制加上運動，可以減少脂肪堆積並增加肌肉量，胰島素阻抗現象及血糖控制皆可獲得改善。然大多數病患仍需藥物治療才能達到治療目標，其中口服降糖藥物的投與仍是方便及有效控制血糖的方式，重點是避免過度治療而導致低血糖的發生，低血糖對心血管及神經認知系統會產生極嚴重的傷害，因此學術團體在制定治療指引時，主張在孱弱的年長者要放寬控制目標，以美國糖尿病學會之指引為例，若合併有嚴重程度的慢性病，例如嚴重心衰竭或是腎衰竭，糖化血色素值可至8.5%，但是對於身心功能俱佳的年長者，其控糖目標仍可比照較年輕族群的7%。當口服藥物療效不理想時，可選擇胰島素注射加強治療效果，此時仍應考量年長者對於較複雜療法之接受度及執行能力。在決定年長者糖尿病的治療策略時，需要多面相的考慮，在達到控制血糖目標與避免低血糖之間需求取平衡。