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Review

Pathophysiology of diabetes in elderly people

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Abstract. The increasing proportions of older persons accounting for global populations, and the implications for increasing rates of chronic diseases such as type 2 diabetes mellitus, continue to be a cause of concern for clinicians. Considering that older persons are a very heterogeneous group of individuals, the management of type 2 diabetes is particularly challenging. Once type 2 diabetes is diagnosed, the principles of it's management are similar to those in younger patients, but with special considerations linked to the increased prevalence of comorbidities and relative inability to tolerate adverse effects of medication and hypoglycemia. In addition, there are clinical aspects complicating diabetes care in the elderly including cognitive disorders, physical disability and geriatric syndromes, such as frailty. Available anti-diabetic oral drugs include insulin secretagogues (meglitinides and sulfonylureas), biguanides (metformin), α-glucosidase inhibitors, thiazolidinediones (TZDs) and newly introduced glucagon-like peptide-1 (GLP-1) analogues and inhibitors of GLP-1 degrading enzyme dipeptidyl peptidase-4 (DPP-4). Unfortunately, as type 2 diabetes progresses in older persons, polypharmacy intensification is required to reach adequate metabolic control with the risk of adverse effects due to age-related changes in drug metabolism. The present review discusses the European Diabetes Working Party guidelines for type 2 diabetes in older persons with and without frailty and their importance on preventing or at least slowing down diverse aspects of disability. (www.actabiomedica.it)

Key words: Diabete, aging, metabolic control

Introduction

There is a continuous increase in the prevalence of type 2 diabetes especially in persons over 65 years of age. The rate of occurrence of this disease increases from 1% to 2% among persons aged from 20 to 39 years to up to around 20% in those aged 60 to 74 years (1). Most patients with diabetes have the type 2, or non-insulin-dependent, form of this disorder, and nearly half of all persons with type 2 diabetes are aged over 65 years (2). This association between an aging population and increasing prevalence of type 2 diabetes is of particular concern because modern diabetes care systems for older people require integrated care with a multi-dimensional approach focusing on preventing diabetic complications, early intervention for vascular disease, and disability assessment.

The European Diabetes Working Party guidelines for type 2 diabetes in older persons was established in December 2000 to ensure that older people in societies across the European Union have consistent and high quality diabetes care throughout their lives (3). These guidelines specifically take into consideration the importance of the frailty syndrome in older persons with diabetes. In this review, we will outline the effects of aging on metabolic control in patients with type 2 diabetes mellitus, and the importance of the guidelines for type 2 diabetes in older persons at risk of disability. We describe some of the available anti-diabetic oral agents used in older persons, including recent drugs such as, the dipeptidyl peptidase-4 [DPP-4] inhibitors, sitagliptin and vildagliptin, and their potential advantages on preventing disability. The metabolic and clinical advan-

tages of diverse anti-diabetic oral agents on tolerability and quality-of-life benefits as well as mechanisms on preventing disability in older persons with type 2 diabetes will also be discussed.

Diabetes in the Elderly

The diagnosis and treatment of type 2 diabetes in older persons poses unique challenges. Due to physiologic changes associated with aging, an elderly patient with type 2 diabetes may not present classic symptoms. Many age-related changes can alter the clinical presentation of diabetes and make its diagnosis problematic. Typical symptoms of hyperglycemia such as polyuria, polydipsia and polyphagia may be masked (4). The renal threshold for glucose increases with advanced age, and glucosuria may not be detected (5). Polydipsia can be absent, and the initial presentation among elderly patients may be dehydration with altered thirst perception and delayed fluid supplementation. More often, changes such as dry eyes, dry mouth, confusion, incontinence or complications relating to diabetes are presenting symptoms. Furthermore, older persons with type 2 diabetes more frequently present functional disability, cognitive decline, increased bone fracture, and hypoglycemic events encompassing comorbid illnesses that contribute to the complexity of type 2 diabetes. Advanced aging is characterized by a number of pathophysiological alterations, which can often lead to frailty. Frailty is a syndrome of decreased reserve and resistance to stressors and is clinically expressed as muscle weakness, poor exercise tolerance, factors related to body composition, sarcopenia, and disability. Indeed, a further problem occurring in the elderly is a tight junction between age-related metabolic changes and the occurrence of co-morbidities which might be responsible for the development of frailty syndrome. Even though, the downward spiral of frailty is activated more quickly in older persons with type 2 diabetes, it is reversible with appropriate interventions before reaching a high level of severity (6). The hazard for geriatric patients with type 2 diabetes is that frailty may compound some of the complications that are already associated with or caused by their diabetes. Frailty is in itself associated with cognitive impairment, reduced ability to perform activities of daily living, increased expression of inflammatory and coagulation markers that may contribute to the adverse microvascular effects of diabetes (7-9). Although metabolic control is the main target in older persons with type 2 diabetes, frail individuals are a specific group in need of improving diverse clinical features during initial therapy with oral anti-diabetic agents. Therefore, the prescription of an anti-diabetic treatment in these individuals must take into consideration not only the standard goal of lowering hyperglycemic levels, but also treating the additional features described above. As illustrated in figure 1, European Diabetes Working Party has added the significance of the frailty syndrome to their guidelines. In particular, the metabolic target range of HbA1c is: <8% in the presence of frailty while in non-frail the range is: <7%. Another important parameter that the guidelines specifically take into consideration is the risk of severe hypoglycemia and it's role on starting anti-diabetic oral treatment (Figure 1).

Available oral agents and limitations for diabetes in older adults

Oral anti-diabetic agents available today include: insulin secretagogues (meglitinides and sulfonylureas), biguanides (metformin), α-glucosidase inhibitors, thiazolidinediones (TZDs). Although such agents have established short-term beneficial effects, none have successfully demonstrated a lasting effect on β-cell dysfunction. Unfortunately, as type 2 diabetes progresses, polypharmacy intensification is normally required to maintain adequate glycemic control, carrying with it an increased risk of adverse events, especially in older persons. Indeed, the changes in normal metabolism of drugs with age and the development of other pathologies make it important that these drugs are prescribed with care in older patients.

Metformin lowers blood glucose levels by sensitizing the liver to the effects of insulin, thus suppressing hepatic glucose output. It also has mild effects on promoting glucose utilization. A recent study found that metformin therapy (either alone or in combination) lowered all-cause mortality rates in a large sam-

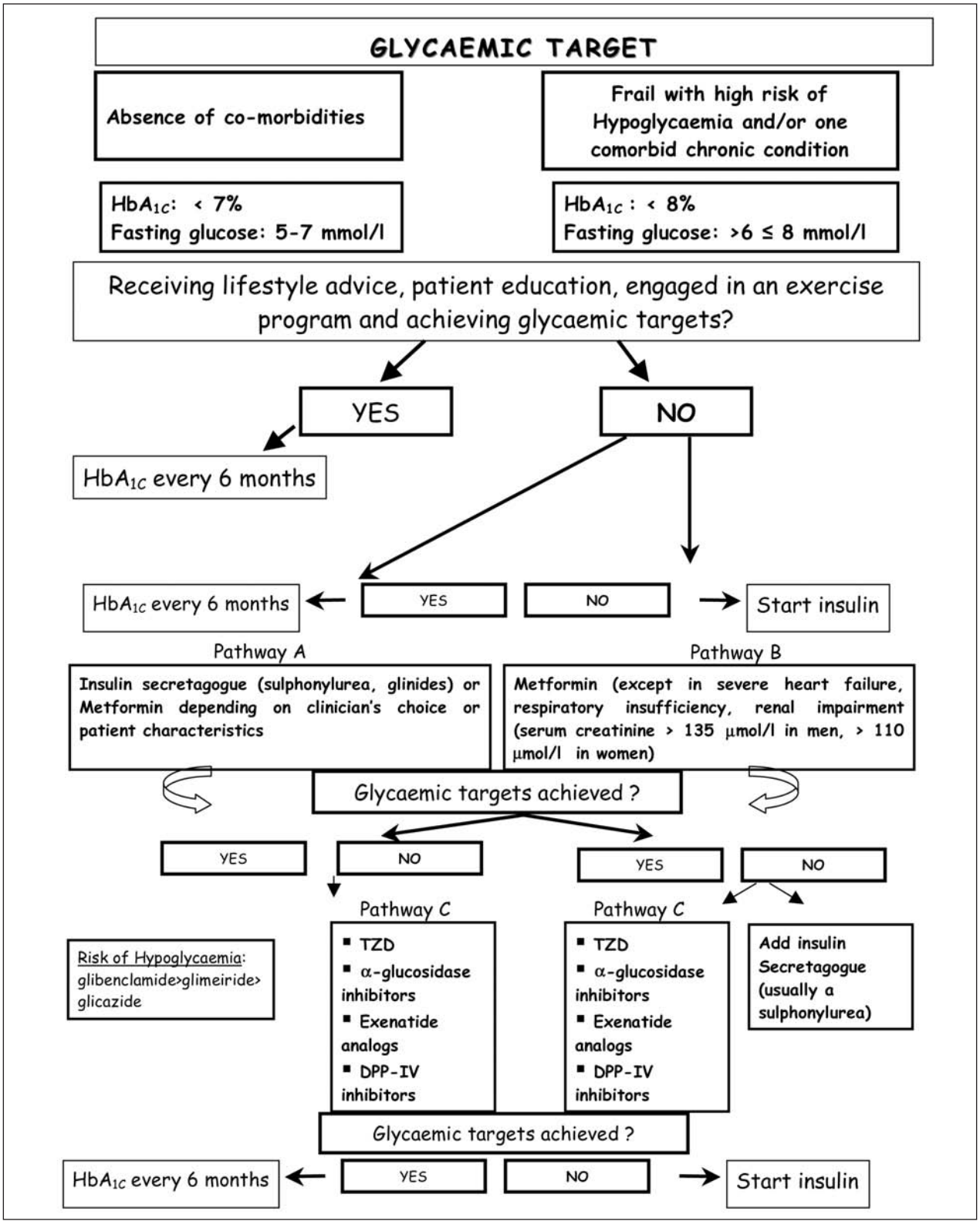

Figure 1. European Diabetes Working Guidelines for Type 2 Diabetes in Older Persons

ple of older type 2 diabetics (10). Metformin in combination with insulin has been shown to be advantageous in avoiding weight gain and hypoglycemia, but is associated with gastrointestinal side effects such as nausea, diarrhea and abdominal pain, which are clearly dose dependent, especially in elderly people (11). The reason that metformin-treated subjects lose weight or avoid weight gain is not completely understood; however, anorectic properties with associated reduced caloric intake have been reported. Therefore, treatment with metformin in older frail adults with type 2 diabetes could worsen age-related changes in caloric intake. Furthermore, metformin must be avoided in those at an increased risk of lactic acidosis, such as those with renal impairment, hepatic dysfunction, congestive heart failure and metabolic acidosis, all common clinical problems found in older persons. Metformin may also cause B_{12} malabsorption which can be extremely crucial for patients with peripheral neuropathies.

Sulphonylurea drugs remain an effective means of achieving blood glucose control after failure of dietary therapy alone in older patients. However, severe symptomatic hypoglycemia is the most serious adverse effect of sulphonylurea drugs that becomes progressively more likely with increasing age due to decreasing renal function. Thus, older patients with type 2 diabetes are more liable to develop hypoglycemia than younger diabetics. In figure 1, it is also highlighted which sulphonureas have been reported to be associated with more numerous hypoglycemic events.

The American Geriatric Society clinical guidelines on anti-diabetic oral treatment in elderly people report that short-acting anti-diabetic agents are preferable to longer-acting agents, due to an increased risk of hypoglycemia (12). Repaglinide is an insulin secretagogue with a rapid onset and relatively short duration of action, and several studies have shown repaglinide to be a safe and effective treatment for type 2 diabetes (13). A recent study reported the safety and effectiveness of short-term treatment with repaglinide, with additional important benefits in terms of lower risk and frequency of hypoglycemia in 88 older patients with type 2 diabetes (14).

In older persons, TZDs improve insulin sensitivity by enhancing insulin-mediated glucose disposal via activation of peroxisome proliferator-activated receptor γ (PPAR γ). TZDs are often thought more suitable therapy for elderly patients because of a decreased risk of the lactic acidosis and hypoglycemia associated with metformin and sulfonylurea therapy (15). Interestingly, treatment with TZDs was not associated with an increased risk of mortality for cardiac events and congestive heart failure compared to metformin (16) and such data was also found in older patients (17). Although TZDs are frequently associated with an increased risk for edema, less gastrointestinal side effects were observed compared to metformin. An unexpected finding with TZD therapy was an increased risk of bone fracture in post-menopausal women in therapy with rosiglitazone, which might be due to an increase in reabsorption of bone mass and a decline in bone density (18). This finding still needs to be confirmed in larger clinical trials aimed at investigating the appropriate use of TZDs in women with T2DM and a family history of bone density alteration.

Incretin hormones such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotrophic peptide (GIP) improve the sensitivity of both the β- and α-cells to glucose, resulting in more insulin secretion from pancreatic β-cells and less glucagon secretion from α-cells in hyperglycemia. GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4). The recently introduced category of anti-diabetic treatment includes the use of incretin hormones as therapeutic agents by either subcutaneous injection of GLP-1 receptor agonists (that are resistant to DPP-4 inactivation) or by oral use of inhibitory DPP-4 enzyme with a relative increase in circulating levels of GLP-1. The two main categories of incretin therapy currently available are: GLP-1 analogs (exenatide) and DPP-4 inhibitors (Vildagliptin, Sitagliptin).

The importance of anti-diabetic oral agents on disability in older persons.

Once type 2 diabetes is diagnosed in those aged 65 years and over, it is important to assess the patient's overall health profile. There are a number of interacting and overlapping conditions that are common in

the elderly which complicate the management of diabetes in this group. Besides diabetic vascular complications, there is also an increased risk for cognitive disorders, physical disabilities and complex geriatric syndromes. There are numerous data in the literature demonstrating that older persons with type 2 diabetes are at a significantly higher risk of disability (Table 1).

The term 'physical disability' is wide-ranging and, in the elderly, can encompass mobility loss, slower walking speed and performance, as well as disability arising from falls and fractures. Type 2 diabetes is consistently reported as one of the strongest correlates of poor lower extremity performance (19-20), mobility loss (21) and falls (22). The risk of developing poor physical function and severe disability is significantly higher in older persons with type 2 diabetes than in nondiabetics even after adjustment for pre-existing complications (23-24). With respect to other physical disabilities, research has shown that elderly persons with type 2 diabetes are two to three times less able to walk 400 meters, prepare meals or do housework than their age- and sex-matched nondiabetic counterparts. (21) The biological mechanisms by which diabetes is associated with a decline in lower extremity function may be linked to increased inflammatory states, reduced metabolic control, and motor neuropathy which lead in turn to disability through micro- and macrovascular complications and significant reductions in muscle mass. Therefore, an accurate use of anti-diabetic oral agents in older persons capable of obtaining good metabolic control may potentially lower the risk of physical disability.

It is also widely known that older persons with type 2 diabetes are more likely to experience cognitive decline than those normal glucose tolerance (25-28). Indeed, diabetes has also been shown to increase the risk of dementia in older persons and the emerging view is that the diabetic brain encompasses many aspects of "accelerated brain aging" (29). Previous reports have clearly indicated that an improvement in fasting plasma glucose and HbA1c levels were associated with an improvement on some neuropsychological tests (30-33), thus indicating that cognitive deficits observed in untreated older persons with type 2 diabetes appear to be attenuated by drug treatments known to improve glycemic control such as rosiglitazone, metformin, sulfonlyureas.

More recent data have demonstrated that postprandial glucose excursions (PPG) of older individuals with type 2 diabetes are also associated with a derangement of both global, executive and attention functioning over time (34). In particular, older patients were randomized to be treated with either glibenclamide or repaglinide and underwent neuropsychological testing every 3 months for 12 months. At baseline, the coefficient variation of PPG (CV-PPG) was associated with Mini Mental State Examination (MMSE) scores ($r= -0.3410$; $p<0.001$) and a composite score of executive and attention functioning ($r= -0.3744$; $p<0.001$) after adjusting for multiple confounders. Both groups showed a significant decline in Hb1Ac and FPG, but only the repaglinide group demonstrated a significant decline of CV-PPG over time. In models investigating the change in cognitive functioning over time, adjusted for HbA1c and CV-FPG, a decline in cognitive functioning was observed only in the glibenclamide group ($p<0.001$). After adjusting for CV-PPG, a decline was no longer

Table 1. Studies testing correlations between type 2 diabetes and disability measures in older persons

Author (year)	n° of subjects	Mean Age (yrs)	Disability measure
Gregg et al (2000)(21)	1030	70.5	Physical disability
Volpato et al (2002)(19)	1002	78.8	Lower extremity disability
Schwartz et al (2002)(22)	629	73.7	Falls, handgrip strength, lower extremity strength,cognitive impairment
Volpato et al (2003)(20)	729	77.4	Lower extremity performance
Yaffe et al (2004)(28)	564	68.2	Cognitive impairment
Abbatecola et al (2006)(34)	156	74.4	Cognitive impairment

found in executive and attention functioning composite score (p=0.085) or the MMSE (p=0.080) with glibenclamide. Despite the fact that better glycemic control was reached in both treatment groups, only those undergoing treatment with repaglinide did not have a significant decline in cognitive performance at 12 months. Therefore, a tight control on post-prandial glucose seems to have an important role on cognitive disability in older persons with type 2 diabetes.

At the moment there is very little data regarding the use and efficacy of incretin therapy (exenatide, sitagliptin) in older persons with type 2 diabetes. However, there is recent information regarding the efficacy of vildagliptin in patients aged 65 years. (35-37) Compared to younger patients, older vildagliptin recipients experienced similar reductions in HbA1c, fasting plasma glucose and body weight and vildagliptin was well tolerated with rare hypoglycemic events(34). Baron et al. (37) pooled data to investigate the effects of vildagliptin in treatment-naïve elderly patients in 174 participants that were administered vildagliptin monotherapy for either 24 or 52 weeks. Following treatment, HbA1c levels were reduced by approximately 1% from baseline levels, similar to changes observed in patients aged below 65 years. In accordance with Pratley et al (35), the incidence of hypoglycemia was below 1% (37).

Conclusions

Older persons with type 2 diabetes are at an increased risk of frailty, cognitive decline, and physical disability. The European Diabetes Working Party guidelines for type 2 diabetes take into consideration the importance of the frailty syndrome and the use of such guidelines suggests important and potential advantages on preventing disability in older persons.

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