PHARMACEUTICAL INTERVENTION IN DIABETIC GERIATRIC PATIENT

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ABSTRACT

The prevalence of type 2 diabetes is expected to Increase gradually with the prolongation of population Aging and life expectancy. In addition to macrovascular and microvascular complications of elderly patients of Diabetes mellitus, geriatric syndromes such as cognitive impairment, depression, urinary incontinence, Falling, and polypharmacy are also accompanied by Aging. Individual functional status in the elderly shows Heterogeneity so in these patients, there are many unanswered questions about the management of diabetes treatment. The goals of diabetes treatment In elderly patients include hyperglycemia and risk Factors, as in younger patients. Comorbid diseases and Functional limitations of individuals should be taken into consideration when setting treatment targets. Thus, Treatment should be individualized. In the treatment of Diabetes in vulnerable elderly patients, hypoglycemia, Hypotension, and drug interactions due to multiple drug Use should be avoided. Since it also affects the ability to self-care in these patients, management of other Concurrent medical conditions is also important.

KEYWORDS: Diabetes Management, Geriatrics, Telemedicine, Elderly.

INTRODUCTION

In 2014, the global prevalence of diabetes, according to The International Diabetes Federation, was 8.3% and 7.9% in Europe (20-79 years).[1] In Portugal, the prevalence was 12.9% in 2013,[2] whereas in the Algarve region there was 11% diagnosed diabetics in 2009.[3]

Diabetes mellitus is a metabolic disorder characterized by A state of chronic hyperglycaemia resulting from abnormalities in insulin secretion, in its action, or both, accompanied By a disturbance in the metabolism of carbohydrates, lipids, and proteins.[4]

The aging of the world's population and ongoing diabetes and obesity epidemics are impacting healthcare worldwide. By 2020, there will be 2 billion adults aged 60 and older, and at least one Out of four will have diabetes[1,2] with overweight or obesity.[3,4,5] Diabetes is chronic and progressive, and its prevalence increases with aging.[6] Younger adults usually endure less Multimorbidity or risk for physical or cognitive dysfunction, albeit some present with complex clinical scenarios. However, their older counterparts usually face more challenges beyond traditional diabetes-related issues, due to the overlap with the aging process and age-related or age-dependent diseases.[7] The elderly Present the highest rates of diabetes-related major lower extremity amputation, myocardial infarction, visual impairment, and end-stage renal disease,[8] cognitive dysfunction, falls, fractures,[9] dementia,[10] cardiovascular (CV) events,[11] malignancies,[12] depression,[13] physical disability, sarcopenia,[14,15] and frailty, which is associated with increased mortality. Furthermore, implementing standard pharmacologic interventions to coexistent multimorbidity might inevitably result in Polypharmacy, with increased costs and risk for non-adherence and medication-related complications.[19] Consequently, the approach to treating diabetes in older adults must encompass all the Abovementioned factors, as they can hinder the ability to perform Diabetes self-management and increase treatment errors, hypoglycemia, and poor glycemic control.[20–22]

Diabetic characteristics in the elderly population

Glucose intolerance increases progressively by aging and the characteristic feature of diabetes in elderly Patients is especially postprandial hyperglycemia. Decrease in beta-cell-compensatory capacity with Advancing age, leads to insulin resistance and it appears As a postprandial hyperglycaemia in the elderly.[7] Therefore, the prevalence varies according to the tests Used during diagnosis on elderly patients. One third Of the individuals who are tested with A1C or fasting Plasma glucose (FPG) are cannot get a diagnosis.[8] The incidence of DM increases with aging. As a result,

Adults may be diagnosed incidentally after the age of 65, or may have had a diabetes diagnosis in middle Age or earlier onset. Having different demographic and Clinical characteristics of these two groups may cause Confusion caused by the setting of the general treatment Recommendations. Age-related DM is characterized by lower A1C the less use of insulin, with frequent occurrence in non-Hispanic whites. In comparison adults with diabetes diagnosed in middle age, the retinopathy Story is more prominent in late-onset diabetic cases, And interestingly there is no difference in prevalence of cardiovascular disease (CVD) or peripheral neuropathy according to age at onset.[9]

Long term complications
Long-term complications of DMT2 can be divided into Two types: micro and macro-vascular complications. Macrovascular complications refer to adverse cardiovascular events Due to atherosclerosis. Patients with DMT2 have a 2-4 times Greater risk of a cardiovascular event (particularly coronary Events) compared to individuals without diabetes.[11-13] Some studies unequivocally demonstrate the association between type 2 diabetes and a history of acute myocardial infarction in terms of cardiovascular risk.[12,14] However, Macro-vascular complications are not limited to the heart: Cerebrovascular diseases such as stroke and peripheral vascular disease also show a higher incidence in patients with type 2 diabetes, than in the general population.[15] Evidence Shows that the relationship between hyperglycaemia and Macro vascular complications is much more complex and less conclusive than those that demonstrate the relationship Of micro vascular complications. This is partly due to the Fact that these macro-vascular complications are not specific to diabetes, but occur more frequently, with greater intensity and sooner, in people with diabetes than in non-diabetics.[16,17] Moreover, there is no clear association between Glycaemic control and cardiovascular disease, since strict Control does not seem to reduce cardiovascular risk in clinical trials.[18] The clinical objectives of diabetes management regarding macro-vascular complications are mainly Focused on avoiding or reducing cardiovascular events. Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality in individuals with diabetes, since the conditions that co-exist with DMT2 (hypertension and dyslipidaemia) are clear risk factors for cardiovascular disease.[19]

Therapeutic interventions
Lifestyle modifications (healthy diet, physical activity, and Exercise) are feasible to implement, and older adults can still Benefit from modest intentional weight loss.[20,21] The Montana Cardiovascular Disease and Diabetes Prevention Program showed older adults had higher lifestyle participation and self-monitoring rates than younger subjects.[22] A recent study randomly allocated 160 mildly-to-moderately frail, sedentary, older adults with obesity, to aerobic, resistance or combined training.[23] While this RCT did not focus on diabetes Alone, intentional weight loss plus combined aerobic and resistance exercise were the most effective interventions for improving functional status. We recommend a future review of Two ongoing RCTs that will evaluate dietary protein[24] and multi-modal interventions for frailty[25] in older patients with type 2 diabetes (T2D). Pharmacologic therapies for chronic diseases involve long-term safety and tolerability, especially in the elderly, with aging and disease-related changes in pharmacokinetics and pharmacodynamics. While we did not see the introduction of a new Antihyperglycemic medication class, there is a greater focus on Understanding CV benefits (or risks) from these medications.

Metformin
Metformin remains the first-line therapy for T2D. A recent systematic review identified 4 interventional and 11 Observational studies, most subjects aged $\geq$ 65.[26] The Efficacy and safety of metformin was better than alternatives, albeit more studies are needed in people $\geq$ 80 years. A cohort study in US Veterans aged 65–89 compared the Mortality between metformin and sulfonylurea users. Metformin was associated with a 30% decreased mortality Risk among those without any frailty-related diagnoses. An ongoing RCT is testing metformin as a novel intervention for frailty prevention.[27]

Sulfonylureas
A 2015 systematic review and meta-analysis of 18 studies using sulfonylureas found greater CV-related mortality with glibenclamide, and lower with gliclazide and glimepiride.[39] There is no evidence to support CV mortality as a drug class. We strongly recommend against the use of glyburide, but still, endorse the use of glimepiride and glipizide for certain patients. These agents are still effective in the older population, with additional benefits due to low cost and access, but we recommend special caution in cases with hypoglycemia risk or uncontrolled obesity.

Geriatric considerations
Geriatric Syndromes and Physical and Cognitive functions
The clinical presentation of an older adult with diabetes is widely Heterogeneous, even for subjects of the same age and similar comorbidities.[8,20,79] Individuals are impacted differently by diabetes, age-related diseases, geriatric syndromes, and aging Itself, showing a range of physical and mental resilience.[80,81] Geriatric syndromes (polypharmacy, urinary incontinence, impaired mobility, falls, frailty, persistent pain, cognitive impairment, and depression) increase the clinical complexity,[82] not only impacting the targets, but also the ability to care for oneself And implement diabetes self-management. Providers can uncover These limitations by assessing the physical and cognitive functions, economic, family, and social support, and geriatric Syndromes. The American Diabetes Association (ADA) Guidelines recognize the

need to incorporate geriatrics components into the assessment and management of diabetes,[84] and Its chapter focused on the older adult reflects the consensus the ADA made with the American Geriatrics Society.[8] The framework for HbA1c-target individualization includes functional and Cognitive status, falls, and urinary incontinence. For patients with Well-preserved physical and cognitive functions, absent life-threatening diseases, longevity in the family, or expected long Life-expectancy, the HbA1c-target category is 6.5–7.5%, similar to younger adults. The inability to complete ≥ 2 Instrumental Activities of Daily Living or IADLs (shopping, cooking, household cleaning/laundry, telephone use, managing medications, finances, and driving/using public transportation), supports a HbA1c-target category of 7.5–8.0%. Limitations in ≥ 2 Activities of Daily Living or ADLs (dressing, toileting, bathing, grooming, eating, and getting around the home) are consistent with the highest case complexity, with HbA1c-target category of 8.0–8.5%.

Geriatric syndromes
Older patients with diabetes, compared to counterparts without, have an increased risk for multiple geriatric syndromes, including falls, urinary incontinence, cognitive decline, and even possibly frailty syndrome. Beyond the increased falls risk due to Age-related decline in posture, balance, gait, and proprioception, Diabetes alone worsens this risk by 17-fold.[88] Examples Include impaired gait with diabetic peripheral polyneuropathy, Diabetic peripheral vascular disease, amputations, neuropathic Pain, impaired vision with diabetic retinopathy, impaired judgment with diabetic cognitive decline, and dementia, Polypharmacy, and hypoglycaemia.[89] Moreover, the elderly with diabetes have poor bone quality and greater vulnerability to fragility fractures.[90] Falls risk is greater in those receiving Insulin.[91] Screening can and should be performed at every visit, especially in those at risk for hypoglycemia or osteoporosis. While standard testing could be performed in minutes. The providers can also detect quickly those at greatest risk by Asking if they have fallen, and observing gait and balance while Walking into the office. These cases will benefit from a Multifactorial risk assessment (a falls clinic).[92] Urinary incontinence is associates with poor quality of life, Depression, disability, morbidity, and mortality,[93] with Greater prevalence in older patients with diabetes, especially In those with mobility and cognitive impairment.[94] Providers ought to recognize the need to: (1) rule out that its Etiology is hyperglycemia, in which case, enhanced Antihyperglycemic interventions should follow, (2) incorporate its presence in the selection of pharmacologic therapies (e.g., avoid SGLT-2i with established, unresolved urinary incontinence), and (3) facilitate communication with the primary care provider towards for a referral to the pertinent Specialist.

Lifestyle changes
Counselling should be provided on all elderly diabetic Patient lifestyle changes (exercise, diet, behavioural Changes, and weight loss in patients who need it). In Elderly diabetic group response to the lifestyle changes (low fat diet and 150 min/wk exercise) were found to Be higher than the young diabetic age group according To the diabetes protection program (DPP).[19]

Physical activity
Elderly diabetic patients should Be guided to activities according to their functional Capa-cities. Prior to physical activity, high-risk, symptomatic individuals with coronary artery disease should be evaluated with electrocardiograms and/or cardiac tests. Functionally independent individuals are offered a Moderate aerobic activity of at least 5 d for 30 min each Week. Besides this, patients with high risk of falling should Be directed to physiotherapists for balance and muscle Strengthening exercises before workouts.

Medical nutrition therapy
All elderly diabetic patients Should be given medical nutrition education and Treatment should be adjusted to their individual needs. When preparing the eating plan, age-related person-specific differences (deterioration in taste, additional Illnesses, dietary restrictions, impaired gastrointestinal function, reduced ability to shop, and reduced food Preparation capacity) must be considered.

Medical therapy
In elderly diabetic patients, lifestyle changes is recommended with metformin for treatment, primarily because of the risk of hypoglycemia, unless there is a Con-traindi-cation (renal failure and unstable/acute heart failure).[20] However, patients with the comorbid disease, multiple drug use, or HbA1c levels close to target levels should be monitored for 3-6 months with lifestyle changes before initiation of metformin therapy.

Insulin formulations
The DURABLE trial was a 30-month multicenter RCT, where 258 patients were assigned to insulin lispro mix 75/25 (intermediate- and short-acting) and 222 patients to glargine insulin. After 24 weeks, the group in the lispro mix presented slightly better HbA1c levels and slightly higher percentages of patients achieving target HbA1c < 7.0%, more weight gain, and higher rates of overall hypoglycemia, but lower rates of nocturnal hypoglycaemia.[21] Newer long-acting formulations of basal insulin, glargine 300 units/mL,[22] and degludec 100 units/mL and 200 units/mL[23] are at least as effective, and with less risk for hypoglycemia. These formulations could be considered when hypoglycemia persists despite clinical efforts to minimize the risk. Notably, one suggested that long-acting formulations could be beneficial for patients having issues with insulin self-injection.[24]

Insulin therapy

In the elderly with poor glycemic control, HbA1c level >9% (74.9 mmol/mol), FPG level > 250 mg/dL (13.9 Mmol/L), randomized glucose value > 300 mg/dL or Patients with ketonuria, insulin should be selected as Initial therapy. When starting insulin therapy in elderly patients, it is important to have general health status, ability to make insulin, to measure blood sugar, to understand hypoglycemia and the capacity to treat it. In the study of geriatric patients using basal insulin and OAD, treatment-related satisfaction surveys and post12-week follow-up in the insulin treatment group showed Significant improvement in the geriatric depression scale (SOURCE).[25] In another study, geriatric patients were divided into OAD treatment with basal insulin addition and elevated OAD dosage group, and a 24-month follow-up Revealed a lower frequency of hypoglycemia in the basal Insulin group.[26] When the ready mixed insulins are evaluated, they are more effective for the control of postprandial glycemia, but they are more useful for the patients who live in the Nursing home, who eat regular meals.[27]

New oral glucose-lowering agents are less likely to Have all-cause mortality, CVD, and severe hypoglycemia When compared to insulin. Dapagliflozin has both decreased mortality due to all causes and reduced CVD Risk, while DPP-4i has been found to be weaker in the decrease of all cases due to mortality.[28]

Elderly patients have their own nutritional needs. Along with the increased age, the taste and odor sensations diminish, as well as changes in the threshold of thirst. For this reason, the balance bet-ween pre-meal insulin and oral food intake should be well established in elderly Patients.[29] Insulin dose reduction should be done according to the number of carbohydrates taken at meals, for example, if half of the meal is consumed, insulin will be Reduced by 50%, insulin will not be administered or 25% Can be administered to patients who consume less than That or may skip meals due to medical intervention. In addition, patients with enteral or parenteral nutrition Should be monitored for glucose at 4-6 h intervals to Avoid hypo hyperglycaemia.[30]

Cardiovascular outcomes
Positive effect

The multicenter Empagliflozin, cardiovascular outcomes, and Mortality in T2D trial (EMPA-REG) randomized 7020 participants to daily empagliflozin 10 or 25 mg or placebo.[31] Empagliflozin had 38% relative risk reduction (RRR) in CV Mortality, 35% RRR in heart failure hospitalization, and 32% RRR in any-cause mortality. A post hoc analysis of phase III Studies with empagliflozin found blood pressure (BP) reduction and improved arterial stiffness and vascular resistance.[32] The multicenter Canagliflozin Cardiovascular Assessment Study (CANVAS) randomly assigned 10,142 subjects to Canagliflozin or placebo.[33] Canagliflozin reduced CV mortality, nonfatal myocardial

infarction, or nonfatal stroke. Other Studies with canagliflozin showed prevention of CV events and heart failure. Six hundred and sixty-six subjects With T2D and heart failure risk were randomized to Canagliflozin (100 or 300 mg) or placebo, to evaluate CV Biomarkers during 2 years.[34] At 26, 52, and 104 weeks, Canagliflozin delayed the rise of N-terminal pro-B-type natriuretic peptide (-15.0%, -16.1%, and -26.8%) and highsensitivity troponin I (-8.3%, -11.9%, and -10.0%), all with $P < 0.05$. A phase 3b RCT will evaluate if dapagliflozin may Reduce major CV events.[35]

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial found Lower CV and all-cause mortality rates with liraglutide Compared to placebo.[70] Semaglutide showed a lower composite rate of CV mortality, nonfatal myocardial infarction, or Nonfatal stroke when compared to placebo, but no significant Difference in all-cause mortality.

A recent meta-analysis showed that SGLT-2i and GLP-1RA were associated with lower all-cause mortality than DPP-4i or placebo.[35] On the other hand, an analysis of The BARI 2D study, which recruited 2368 subjects with diabetes and stable heart disease, showed greater CV (16 vs 11%, $P = 0.04$) and all-cause-mortality (HR 1.89, 95% CI 1.1–3.2, $P = 0.02$) in subjects aged ≥ 75 years who received exogenous Insulin or insulin secretagogues instead of insulin-sensitizing Therapies, whereas younger subjects did not show mortality differences between these approaches.[36]

Netural effect

Studies on other GLP-1RAs did not show similar results, suggesting that the benefits may not be a class effect. The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial did not find a reduction of major CV events or Death with the addition of lixisenatide.[74] Similar neutral findings were observed in studies with once-weekly Dulaglutide[75] and exenatide. Studies addressing the potential role for DPP-4 inhibitors Did not find evidence to support that this class of medications Would offer similar benefits. These include studies with Sitagliptin.[37]

Cognitive Impairment and Dementia

Older patients with diabetes are 50 to 100% more likely to Develop dementia, worse if long-standing disease or uncontrolled, and if accompanied by vascular complications. Data from a longitudinal study (median follow up 6.1 years) Was used to compare changes in multiple cognitive functional tests. This study included 3069 adults aged 72 to 96, from Whom 9.3% had diabetes at baseline. Cases with diabetes had Lower baseline executive and global cognition; their rates of Decline did not differ from those seen in patients without diabetes. A recent Cochrane systematic review studied the role of Antihyperglycemic therapy and the progression of cognitive decline.[24] Treatment strategies

included multiple Antihyperglycemic medications and a follow-up period of 40 to 60 months. There was no evidence that any particular Antihyperglycemic strategy prevented or delayed cognitive Impairment. However, using data from 2 studies (12,827 subjects), they observed more episodes of severe hypoglycemia (RR 2.18, 95% CI 1.52 to 3.14) in subjects receiving intensive Therapies, but did not observe differences in mortality.[38]

Integrative and Functional medicine
Functional medicine applies a systems biology approach and expands the attention to contributing factors that affect metabolism and insulin resistance. Some of the factors that have Been studied in the last 5 years are immune dysregulation, Xenobiotics exposure, nutrient deficiency, and gut Microbiome.

Xenobiotics
These are exogenous, potentially toxic substances. Bisphenol A (BPA) and phthalates (both widely disseminated in plastics) Have been associated with an increased risk of diabetes and obesity.

Incretin based medications
Dipeptidyl peptidase-4 inhibitors -
Dipeptidyl peptidase-4 inhibitors (DPP-4I) is a member f a large family of enzymes responsible for the destruction of many GIS hormones, neuropeptides, Chemokines and cytokines. In response to food-borne Carbohydrates, they are secreted from small intestine's K and L cells. They increase pancreatic insulin secretion, Slow down gastric emptying, and suppress the increased postprandial glucagon secretion.[39] DPP-4 inhibitors Are an attractive treatment option for elderly diabetic Patients due to the single daily dose, lack of risk for Hypoglycemia and neutral effect on weight. The most important side effects are headache, nasopharyngitis, Upper respiratory tract infection and acute pancreatitis. Creatinine clearance should be calculated before Treatment in each patient and dose should be reduced If < 50 mL/min. For sitagliptin if Egfr < 30 mL/min For, it should preferably not be used and if the eGFR is Between 30-50 mL/min, the dose should be reduced by 50%. If eGFR < 15 mL/min in vildagliptin, saxagliptin, and linagliptin, they should preferably not be used, But for Vildagliptin if eGFR between 30-60 mL/min or patient has dialyzed it can be used without dosage Adjustment. For Alogliptin treatment, if the eGFR is 30-60 mL/min, the dose is reduced by 50%, whereas if the eGFR is < 30 mL/min, the dose is reduced by 75%.

In the study comparing glipizide and sitagliptin in Elderly diabetic patients, A1C reduction was similar in Both groups, but less hypoglycemic event was encountered in the alogliptin-receiving group.[40] In another study conducted by Scirica et al,[41] the group receiving Saxagliptin treatment in elderly diabetic patients was found to have a higher rate of hospitalization with cardiac Insufficiency. On the other hand; a systemetic rewiew Deduced that incretin-based treatment (agents) does not Increase major adverse cardiovascular events.[42] The effects of the DPP-4 group drugs on the A1C lowering Are insufficient. Therefore, monotherapy can be used in with A1C level close to the target value. They may also be added to metformin, SU and insulin therapy.

CONCLUSION
The management of elderly patients with diabetes presents Unique challenges. A comprehensive evaluation and holistic Approach are required to properly individualize targets and Strategies in this age group. Figure 1 summarizes the concept of incorporating approaches to offer a whole health approach to the older person with diabetes. The recommended approaches are consistent with geriatric.

Principles
- Start low, go slow, and progressively increase towards the Individualized target.
- Follow the best evidence for greater benefits and safer therapeutic profiles.
- Favour agents with the lowest hypoglycemia risk and least Polypharmacy (when possible, avoid multiple times/day Formulations).

When starting OAD or insulin therapy in the elderly, Treatment regimens containing as simple and few drugs as possible should be administered, and drug therapy Should not be initiated unless it is necessary and if necessary must start with low dose and dose increase Should be done slowly. All patients should be evaluated with liver and kidney function tests before onset of Treatment.

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