Endocrinology

22

Willy Marcos Valencia and Hermes Florez

This chapter focuses on frequent endocrinology problems in older adults looking through a "geriatrician prism." The following learning-cases facilitate discussion of pertinent topics:

22.1 Case 1

Mr. F. is a 78-year-old white non-Hispanic patient without any known major chronic disease. His body mass index (BMI) is 29 kg/m^2. He exercises daily, between home and a supervised exercise group program. He remains active at home and volunteers in a local hospital. He reports good memory and enjoys a happy life with his wife. Both his parents survived into their 90s.

22.2 Case 2

Mrs. O. is a 67-year-old Hispanic patient with recently diagnosed type 2 diabetes. She does not have micro- or macrovascular complications but is concerned about being at-risk for them. Her BMI has increased over the past few years, despite her efforts, and currently is 33 kg/m^2. She has tried to be physically active but reports limitations as she takes care of her 7-year-old grandson while her daughter goes to school and work. Her functional status is preserved, but she now manifests features of mild cognitive impairment.

22.3 Case 3

Mr. P. is a 66-year-old African American patient with longstanding type 2 diabetes and metastatic prostate cancer, treated with bilateral orchiectomy 4 years ago. Since then he has been receiving androgen-suppression therapy. His medical history includes controlled coronary heart disease, diastolic heart failure, and embolic stroke, without residual neurological deficits. He complains of weight gain, depression, lack of energy, and has recently become more forgetful. His family (wife, children, and brothers) are supportive, and they usually take turns to come to the appointments.

22.4 Case 4

Mrs. B is a 72-year-old white non-Hispanic patient with type 2 diabetes and coronary heart disease who was recently discharged home from a skilled-nursing facility after completing rehabilitation following hip fracture and replacement. Her BMI is 26 kg/m^2 and she has tolerated her new regimen of medications for diabetes and osteoporosis. She is now at home, where she lives alone, but reports having a number of neighbors who look after her.

The chapter will be presented in four sections addressing the most common endocrinologic problems in the elderly: diabetes (including prediabetes and obesity), osteoporosis (and hypercalcemia), thyroid diseases, and male hypogonadism.

22.5 Diabetes in Older Adults

More than 11.2 million or 26 % of those age 65 years and older have diabetes in the USA [1]. The annual incidence in those ages 65–9 years is 10.5 per 1000 people [2]. Based on Hemoglobin HbA1c (HbA1c) data, the Centers for Disease Prevention and Control (CDC) reported that about 37 % of

W.M. Valencia, MD, MSc (✉) • H. Florez, MD, MPH, PhD
Division of Epidemiology & Population Health,
Department of Public Health Sciences, Miami VA Medical Center,
Geriatrics Research, Education and Clinical Center (GRECC),
University of Miami, 1201 NW 16St., 11 GRC CLC 207 A2,
Miami, FL 33125, USA
e-mail: wvalenciarodrigo@med.miami.edu

J.R. Burton et al. (eds.), *Geriatrics for Specialists*, DOI 10.1007/978-3-319-31831-8_22

US adults adult population has prediabetes, and more than half of them were age 65 years and older [3]. There is growing concern since 1 out of 4 people with diabetes remained unaware of the diagnosis [4]. Similarly, prediabetes has been widely unrecognized, and more than 60 % of those at-high risk for prediabetes are 65 years and older.

Understanding the challenges associated with the diabetes epidemic in this age group is paramount for both endocrinologists and geriatricians. Older patients with diabetes have significant clinical and functional heterogeneity that should impact the choice of pharmacological agents and management targets [5–7]. Most providers recognize the importance of a patient-centered approach considering specific features such as diabetes duration, life-expectancy, comorbidities, complications, attitudes, resources, and support systems [8].

There is variability in the development of diabetes-related complications. Using the clinical vignettes, Mr. F. (Case 1) is at risk of developing diabetes due to his age and high BMI, but has no comorbidities, while Mr. P. (Case 3) has long-standing diabetic macro-vascular complications, metastatic prostate cancer and is experiencing a decline in physical function and depression. These very different patients warrant very different approaches to prevention and treatment. In addition, Mr. P's. clinical presentation is typical of older adults with diabetes that often includes several comorbid conditions that impact functional status, life-expectancy, and increase the risk for side effects and adverse reactions from diabetes interventions [9].

Life-expectancy varies significantly depending on the number and severity of diabetic complications and comorbidities, functional reserve, physical and cognitive function, social support and environment, as well as genetic background (i.e., parental longevity vs. those with family history of premature death). Diabetes duration and advancing age independently predict diabetes morbidity and mortality rates [10]; while an accurate determination of life-expectancy is not possible, an estimation of short, intermediate, and long-term life-expectancy can facilitate establishing goals and the management intensity needed to reach them.

Since there is limited data from clinical trials focusing on older adults with diabetes, it is challenging to implement evidence-based care for diabetes in this age group [11]. Decisions should be individualized using data available from clinical studies, recommendations from clinical guidelines and the clinical experience of the providers.

Most endocrinologists implement a comprehensive approach for diabetes management [12], and include coordination of care and specialized services (ophthalmology, podiatry, nephrology, cardiology, neurologist, home health care, etc.), while involving the patient's family and any other support available. Additional geriatric assessment could improve care, particularly considering the association of diabetes with dementia, dysmobility, and falls. Therefore endocrinologists and other practitioners should consider incorporating cognitive and physical function assessments in their evaluation of older patients [13].

22.5.1 Diabetes and Clinical Inertia

There is growing concern about clinical inertia in older patients with diabetes [14], which may result in either under or over treatment. These can be described with the three different scenarios: (1) resistance to implement early intensive preventive therapies for weight and glucose control in healthy older adults with newly diagnosed diabetes or prediabetes; (2) lack of adoption of current recommendations for the management of older adults with diabetes that tailor targets according to health status, multimorbidity, cognition, and life-expectancy; and (3) lack of awareness of patient's preferences and circumstances related to their functional, mental, and social domains.

The first inertia scenario may occur among primary care providers related to concerns about overtreatment, underestimation of life-expectancy, and low confidence in the ability of older adults to respond to life-style interventions. For example, Mr. F. (Case 1) is at risk for developing diabetes due to his BMI of 29 kg/m^2. He should be screened with a HbA1c, and if in a prediabetic range he would be an ideal candidate for the Diabetes Prevention Program (DPP) [15]. While most clinicians are aware of the efficacy of these programs in younger adults, the benefits from lifestyle improvements are even greater for older individuals [16]. If despite DPP interventions Mr. F develops diabetes at age 78, the recommended HbA1c target would be <7.5 % [5], and lower HbA1c values would be appropriate only if this is accomplished without hypoglycemia and done in consideration of the patient's preferences, access, and support [8]. Using targets similar to the general adult population (HbA1c <6.5 %) [17] may be reasonable for some healthy older adults with short diabetes duration, but may not apply in the patient described here who is approaching age 80. Individualized targets [5–8] require further assessment of physical and cognitive function, life-expectancy, and patient's preferences, and avoids hypoglycemic events.

The second inertia scenario may occur when older patients with diabetes are not treated according to recommendations from the American Geriatrics Society and American Diabetes Association guidelines for this age group [6], which recommend less intensive glycemic control in older adults with diabetes. Even these guidelines were based on major studies that recruited "young" old adults (62.2 ± 6.8 years in ACCORD [18], 66 ± 6 years in ADVANCE [19], and 60.4 ± 8.7 in VADT [20]). For adults in their late 70s and 80s, even great caution and clinical judgment must guide therapeutic targets and interventions, since there are no clinical trials in those age groups.

Finally the third inertia scenario occurs when there is failure to recognize that geriatric syndromes are more common in older people with diabetes. These syndromes (impaired mobility, dementia, depression, etc.) impact the patient's ability for self-monitoring, and others (falls syndrome, osteoporosis, frailty syndrome, poor dentition, malnutrition, etc.) increase the risk for negative outcomes from hypoglycemia or hyperglycemia. Thus, tight glycemic control in the older adult and particularly in the oldest old can be difficult and potentially detrimental.

Table 22.1 illustrates the evolving targets for an older individual whose diabetes progresses, when diabetic complications occur and when there is a decline in physical and cognitive function or when geriatric syndromes develop.

22.5.2 Diabetes and Renal Disease

Progressive loss of renal function is associated with aging although the degree of loss is highly variable. Chronic kidney disease (CKD) is a complication of diabetes or can be associated with hypertension (HTN), another common age-related disease. In addition, older adults may be treated with pharmacologic agents that could lead to kidney damage. Since several anti-hyperglycemic medications (Table 22.2) are renally excreted, the management of older adults with diabetes and kidney disease is challenging, particularly in those with advanced CKD.

The reader is also referred to Chap. 25, Nephrology.

22.5.3 Geriatric Syndromes and Diabetes

Geriatric syndromes are prevalent in older adults, associated with aging and comorbidities, and often lead to poor quality of life, loss of independence, and admission to long-term care facilities [23]. These syndromes include cognitive decline, depression, persistent pain, polypharmacy, urinary incontinence, and reduced mobility and falls. Some of these may impair diabetes self-management, lead to poor glycemic control, and increase the risk for hypoglycemia especially those described below [24].

Table 22.1 Evolving glycemic targets and changes in geriatric domains during diabetes disease progression in the older patient

Clinical Scenario	HbA1c goals ADA and AGS[a]	Comments
Mrs. O. (Case 2) 67-year-old Hispanic patient **Medical** recently diagnosed T2D. **Functional** preserved functional status **Mental:** mild cognitive impairment (MCI). **Social:** lives at home, independent, has family support	<7.5 % Or 6.5–7.5 % As long as no hypoglycemic events	There is potential harm in lowering HbA1c <6.5 % in older adults [19]. Implement lifestyle changes towards modest intentional weight loss. Start low, go slow, with pharmacologic interventions, and monitor; follow up and titrate to reach the target
Two years later, Mrs. O. presents with one or several of the following scenarios: **Medical (1):** a myocardial infarction, and heart failure **Medical (2)**: Parkinson's disease, chronic kidney disease stage 3, and emphysema. **Medical (3):** newly diagnosed colon cancer. **Functional**: requires assistance with ADLs (bathing and dressing) **Mental:** MCI has progressed to dementia **Social:** lives in an Assisted Living Facility which cannot administer insulin four times per day	<8.0 % Or 7.0–8.0 % As long as no hypoglycemic events	Studies support avoiding intensive glycemic control in individuals with macrovascular complications. Similar approach applies in multimorbidity (more than three chronic diseases), cancer, or mild to moderate cognitive impairment, and with two or more Instrumental ADL impairments
Six years later, Mrs. O. presents with one or several of the following scenarios: **Medical (1):** has a massive stroke with major neurological and functional sequel **Medical (2):** develops severe liver damage due to acetaminophen toxicity, and now presents end-stage liver disease **Medical (3):** develops rapidly progressive chronic kidney disease, and requires hemodialysis **Functional:** loss of physical function, bedridden, dependent for most activities of daily living **Mental:** advanced dementia **Social:** admitted to a nursing home Her family requests a focus on quality of life and avoidance of polypharmacy	<8.5 % Or 8.0–8.5 % And up to 9 % in cases unlikely to benefit from lower values, due to limited life expectancy	Higher targets relate to lack of benefit from more aggressive interventions and the need to avoid hypoglycemia. Still aims to avoid severe hyperglycemia and glycosuria, which may be associated with impaired wound healing, infection, and urinary incontinence, volume depletion, hypernatremia, delirium, falls, as well as hyperosmolar hyperglycemic nonketotic syndrome or diabetic ketoacidosis

Goals must be achievable without recurrent or severe hypoglycemia or undue treatment burden. For cases experiencing those, reducing antihyperglycemic medications and allowing higher HbA1c values is appropriate. This recommendation increases in relevance as the clinical scenarios progress to situations with end-organ failure, long-term care, and end-of-life care

Note: HbA1c might not be reliable in severe illness or disease, and targets may be based on measured glucose values

[a]Recommendations based on the American Diabetes Association and the American Geriatrics Society, including individualization of targets and patient-centered characteristics [5, 6, 8, 21]

Table 22.2 Pharmacotherapy for diabetes in the older adult

HbA1c Target based on clinical scenarios In Table 22.1	Management	
	First line	Second line [a]
<7.5 % Or 6.5–7.5 % As long as no hypoglycemic events	Maximize lifestyle interventions. Avoid medications associated with weight gain **Metformin** • May help with weight loss • Start 500 mg PO with largest meal, monitor tolerance, increase slowly, towards target of 1000 mg PO BID • Monitor renal function, counsel patients when to hold medication in settings where renal function may be impaired (procedures using iodinated contrast)	**Glucagon like peptide-1 receptor agonists (GLP-1 RA)** • Reduces appetite, useful if the patient has concomitant obesity • Requires injection (check manual dexterity, vision) **Dipeptidyl peptidase inhibitors (DPP)-4 inhibitors** • Weight neutral • May be preferred if the patient has limitations in vision, or prefers an oral agent • Dose adjust based on renal function; except linagliptin **SGLT-2 inhibitors** • Risk of urinary tract infections and ketoacidosis • Reduces glucose resorption from kidney; caution in patients with urinary incontinence (UI); may cause or contribute to UI. If UI identified, refer to primary care or geriatrics for further evaluation and management **Second generation sulfonylureas** • May cause hypoglycemia and weight gain, start with low dose glipizide or glimepiride, monitor and titrate • Useful when drug cost is important (generics available) • Do not use glyburide [22] which is long acting and has numerous drug interactions • Evolving concern on cardiovascular safety **Basal insulin** for patients who are not eligible or amenable to any of the above options • Start 0.2 units/kg/day, monitor and titrate [16] • Older patients with new onset diabetes and HbA1c above 10 %; patients may not fully respond to oral agents. Start basal insulin and preprandial short-acting insulin
<8.0 % Or 7.0–8.0 % As long as no hypoglycemic events	**Metformin**	**DPP-4 inh** (same as above) **GLP-1 RA** (same as above) **SGLT-2 inh** (same as above) **Insulin**: as above
<8.5 % Or 8.0–8.5 % And up to 9 % in selected cases unlikely to benefit from lower values, due to limited life expectancy	Most non-insulin antihyperglycemic agents will require to be stopped due to limitations in renal excretion and disease status **Begin** • Insulin basal bolus and preprandial • Daily home skilled nursing services not feasible long term • Basal insulin plus oral agents, as long as glycemic target can be achieved **Other considerations** • Use alternatives to insulin if the patient/caregiver cannot check glucose or inject insulin 4 times/day • Most patients with advanced chronic kidney or liver disease require insulin, due to risks, lack of evidence, unpredictability, or contraindications to non-insulin options. • Insulin can be challenging, if caloric intake fluctuates, for procedures, e.g. hemodialysis, etc.	**DPP-4 inhibitor alone** (reduces HbA1c by 0.7 %) consider when this may be sufficient to reach target **DPP-4 inhibitor plus Alpha glucosidase inhibitor (if tolerated)** **Long-acting GLP-1 RA** (weekly), if effective and safe, may be convenient in certain settings, especially when the patient requires assistance with medications **Other considerations** • Avoid glucose values above 220 mg/dl, since this can be associated with glycosuria (dehydration and UI). • Not only avoid glucose values close to 100 mg/dl, but if a trend towards these values is detected, a decrease in the intensity of regimen may be required, before a hypoglycemic event occurs. • Avoid weight loss, which will be mostly be from muscle and bone mass, due to low physical activity levels in many of these patients

[a]With proper monitoring, titrate up as needed to accomplish the desired target

22.5.3.1 Polypharmacy

In prescribing for an older person with diabetes, it is important to recognize that older people may carry chronic diseases from earlier life, as well as develop new diseases, and that multimorbidity leads to being prescribed a great number of medications, with higher risk for drug–drug or drug–disease interactions. In addition, adherence to medications declines as the number of medications and the frequency of dosing increases. Polypharmacy in older people with diabetes has also been driven by pay-for-performance and the use

of HbA1c as a quality outcome measure [25]. Often when providers follow guidelines for a series of conditions, the result is polypharmacy. Guidelines are not based on studies of patients with multimorbidity. The recent shift toward quality outcomes that include reduction of polypharmacy by incorporating age- and patient-specific factors to assess quality and performance should lessen medication burden [26].

The American Geriatrics Society published the "Beers criteria," a list of medications that should be avoided or used with caution in older patients [22]. Among them, Glyburide is listed as a drug to avoid, as it is associated with a high risk for hypoglycemia due to its long half-life. While sulfonylureas may have decreased due to new alternative agents, it these agents are still sometimes useful. While glyburide ought to be avoided other sulfonylureas (like glipizide or glimepiride) are acceptable. Similarly the routine use of regular insulin sliding scale is discouraged by the Beers Criteria in older adults with diabetes. Table 22.2 presents an overview of pharmacologic options, and considerations in the geriatric population.

22.5.3.2 Cognitive Impairment

There is epidemiological evidence that diabetes increases risk for cognitive impairment [27, 28]. Long-standing diabetes may contribute to the development of dementia, however there are insufficient longitudinal studies to address the impact of patient attrition (i.e., patients with diabetes may not live long enough to develop dementia). The Atherosclerosis Risk in Communities study showed the association between diabetes in midlife and long-term cognitive decline [29], suggesting that diabetes prevention and control in midlife may protect against cognitive decline later in life.

Poor glycemic control with recurrent especially severe hypoglycemic events is independently associated with accelerated late-life cognitive decline [30], and there is no evidence that more intensive glycemic control will slow progression towards dementia.

The Memory in Diabetes study (ACCORD MIND) evaluated patients with type 2 diabetes with a mean age 62.5 years, and showed no benefit from intensive glycemic or blood pressure interventions on cognitive testing [31]. Similarly, an ancillary analysis from the Look AHEAD study showed no benefit in cognitive function after 8 years of intensive lifestyle intervention in adults with obesity and type 2 diabetes [32]. Studies in older adults at high-risk or with newly diagnosed type 2 diabetes may provide better understanding on the potential benefits of earlier interventions to reduce the risk of cognitive decline and preserve function in these patients.

Hypoglycemia in older adults with type 2 diabetes is associated with increased risk for cognitive decline and dementia [33]. Conversely, a post-hoc analysis in the ACCORD study showed that poor cognitive function may increase the risk of severe hypoglycemia [34]. These points emphasize the importance of incorporating cognitive assessment as pertinent to refine a treatment plan and to avoid hypoglycemia in the older adult with diabetes.

The reader is referred to Chap. 8, Office Tools for Assessment for recommendations on screening for cognitive impairment.

22.5.4 Challenges with Insulin Use

Due to the progressive natural history of type 2 diabetes, most patients will eventually require insulin. However, the dexterity and ability needed to implement an insulin regimen could be affected by neuropathy, arthritis, cognitive impairment, and other comorbidities. If self-management skills are limited, then providers should assess the availability of informal (i.e., family or friends) or formal (e.g., home health nursing) support to implement and monitor an insulin regimen. In addition, documenting in the patient's record the presence of these chronic conditions and comorbidities will help providers reach the level of complexity needed for appropriate clinical reimbursement and facilitate coordination of care for older adults with diabetes on insulin.

22.5.5 Challenges with Obesity Management

The prevalence of obesity and its comorbidities increase with age [35]. Obesity could impact the medical (e.g., type 2 diabetes, cardiovascular disease, and cancer), mental (e.g., depression and dementia), social (e.g., stigmatization and isolation), and functional domains (e.g., impaired mobility) in the geriatric population [36–39]. However, the assessment and management of obesity in older adults with diabetes may not be common practice among providers. One contributing factor may be the limited evidence on potential benefits associated with weight loss medications and bariatric surgery in older adults. However, modest intentional weight loss through lifestyle (healthy nutrition and increased physical activity) could reduce the burden of obesity-related comorbidities and improve the quality of life of otherwise healthy obese older adults [36].

The "obesity paradox" is a term used to describe the fact that better outcomes are seen in older people at higher BMIs compared to younger people [40–42]. Epidemiological studies have described better survival in overweight older adults with heart failure, hypertension, stroke, and end-organ damage. However, better outcomes are also seen in each BMI category, when better fitness was also present [41, 43, 44] suggesting that fitness and not simply fatness is important. Therefore, it is important that cardiovascular and physical conditioning with modest weight management should be a part of the plan of care in older patients with diabetes. In

Case 1, Mr. F. who has a BMI of 29 kg/m^2 would benefit from the lifestyle interventions consisting of exercise, and modest intentional weight loss. He may lose 10 lb in 1 year, and lower his BMI to 28 kg/m^2. While remaining in the overweight group, he has likely improved his clinical, metabolic, and functional profiles.

22.6 Osteoporosis and Bone Metabolism

Osteoporosis increases with age but there are potential gender differences in its consequences. Osteoporosis-related fractures are more common in older women, probably related to accelerated bone loss in the postmenopausal period, but mortality is greater in older men within the first year after a hip or femoral fracture [45, 46]. In addition, the prevalence of osteoporosis increases in the oldest old (age 80 and older), in whom the average T-score is lower than −2.5 SD. Furthermore, more than 50 % of patients admitted to a hospital with hip fracture belong to this age group [47, 48].

Among non-communicable chronic diseases, osteoporosis is fifth in disability burden behind coronary heart disease, lung disease, osteoarthritis and Alzheimer's dementia [49]. Therefore, timely assessment and appropriate therapy could reduce the growing burden associated with osteoporosis.

22.6.1 Osteoporosis Screening

Current guidelines provide recommendations for osteoporosis screening for both women (age 65 and older with or without risk factors) [50, 51] and men (age 70 and older with risk factors) [52, 53]. Approximately 50 % of women and 20 % of men are at risk for an osteoporosis-related fracture during their lifetime. Osteoporotic fractures accelerate functional decline in older adults and have major economic impact [54, 55]. The annual costs of incident fractures are estimated at $ 17 billion with men accounting for 29 % of fractures and 25 % of costs. An economic model incorporating the growth of the older adult population projected that by 2025 the annual fractures and costs will increase by 50 % [54]. Forty percent of people who break their hip do not fully recover to their functional level before the fracture and 20 % have such major functional decline that independence is lost and long-term care placement may result [55].

Prevalence studies find nearly half of all women age 80 and older have a vertebral fracture [56]. Additionally, older adults with vertebral fractures present with progressive height loss, pain, loss of mobility and independence, psychological distress, decreased quality of life, and increased risk of disability [57–59]. Furthermore, patients with vertebral fractures also have increased risk for non-vertebral fractures.

22.6.2 Osteoporosis Risk Assessment

In addition to age-related decline in bone, the loss of gonadal function in both women and men, and conditions associated with inflammation may contribute to increased risk of fracture [60–62]. In the World Health Organization (WHO) Fracture Risk Algorithm (FRAX®, available at https://www.shef.ac.uk/FRAX/), increasing age is one of the strongest predictors for fracture risk, only second to personal history or family history of previous fragility fracture. Of interest, there is a remarkable variation in the age-specific risk for fracture worldwide. In the 45 countries studied, there was greater heterogeneity between countries than between gender differences within a country [63]. A revision of FRAX (3.0) uses updated epidemiological information in the USA and shows the predictive value for hip fracture even in men and women age 70 and older [64].

Data from the Osteoporotic Fractures in Men Study (MrOS), suggests that pharmacologic treatment would be needed in one-third of USA; white men aged 65 years and older and one-half of those aged 75 years and older [65]. A practical approach to screening for men is to address height loss, especially if ~1.5–2 in., as potentially associated with asymptomatic vertebral fractures [17]. Additional clinical risk factors that should prompt earlier screening include low body weight, history of prior fragility fracture, family history of osteoporosis, smoking, excessive alcohol intake, and long-term use of high-risk medications (e.g., glucocorticoids at doses >5 mg/d of prednisone, or its equivalent) [66].

22.6.3 Special Considerations in Older Adults

Falls, sarcopenia, and frailty are not included in FRAX, but they are associated with increased fracture risk in older adults [67–74]. In addition, more than 50 % of people hospitalized due to hip fracture are older than 80, and many of those will sustain another fracture [47, 75–78] For patients with spine and hip fractures, there is a broad body of literature supporting the reduction of fracture risk from pharmacological treatment [50]. In general, these medications are safe in the older population as long as pertinent precautions are followed. For instance, in older adults with CKD stages 4 and 5 bisphosphonates are contraindicated, and proper monitoring is required to avoid adynamic bone disease [79, 80] (see also Chap. 25, for a discussion of metabolic bone disease.) However, the alternative antiresorptive monoclonal antibody denosumab could be considered.

Before starting either type of antresorptive therapy, examination of the oral cavity by a dental professional is indicated. This is especially important in the older people who are at greater risk for oral disease (poor dentition requiring dentoalveolar surgery, tooth extraction, dental fractures)

and poor oral health (including periodontal disease, caries, infections) [81]. Oral disease increases risk of osteonecrosis of the jaw. While most cases have been reported after IV formulation in frail older adults with multimorbidity and/or history of malignancy, it is recommended to treatment dental diseases prior to beginning antiresorptives [82].

In addition, calcium and vitamin D supplementation and exercise (see below) are important in prevention and management of osteoporosis [83, 84]. The recommended calcium intake for older adults is 1200 mg per day, ideally from dietary sources [50, 52, 84, 85]. The National Institutes of Health offer a fact sheet for calcium supplementation, with detailed information on dietary sources of calcium (available at https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/#h3). However, the dietary intake of calcium in older adults is usually insufficient (about 600 mg per day), thus prescription supplementation is often required to reach the target (additional 500–600 mg per day). Furthermore, older adults have an increased prevalence of chronic or atrophic gastritis, with achlorhydria, leading to malabsorption of calcium [86]. Therefore, some experts suggest calcium citrate over calcium carbonate [87]. Constipation may develop with either, and it is important to advise proper hydration and measures to avoid this geriatric syndrome. Concomitant intake and maintenance of proper vitamin D is required to ensure calcium absorption. However, older adults commonly have low levels of 25 hydroxyvitamin D (25OHD) and, in spite of reports of measurement inconsistencies [88, 89], this should be measured. Vitamin D supplementation is recommended when levels are below 30 ng/ml, aiming to maintain levels above 35 ng/dl using D3 (cholecalciferol) [90, 91]. Toxicity is rare, as vitamin D has a wide therapeutic range. Additional potential benefits of vitamin D repletion include reduction of falls and improvement of physical function [51, 89, 91].

There is evidence of the effectiveness of exercise to preserve or improve bone mass and also to reduce falls [92–94]. Falls are reduced particularly with the combination of aerobic, flexibility, resistance and balance training. Exercise recommendations must be tailored, especially for those with severe osteoporosis, who should avoid forward flexion exercises, using heavy weights, or side-bending exercises, because pushing, pulling, lifting, and bending exert compressive forces on the spine that may lead to fracture. These patients may benefit from specific recommendations provided by a physical therapist [50]. For the majority of older patients, at risk for or with osteoporosis, resources include the National Institute on Aging Go4Life program, which offers free education materials (available at https://go4life.nia.nih.gov) [95] and the National Council on Aging, which lists a number of evidence-based programs (available at https://www.ncoa.org/center-for-healthy-aging/physical-activity/physical-activity-programs-for-older-adults/) [96].

For primary prevention of fractures, a patient with known osteoporosis should have an assessment of gait and balance, especially if there is a history of falls. For details see Chap. 8 on Office Based Assessment. While not specific to osteoporosis, the practice guidelines from the American Geriatrics Society and the British Geriatrics Society [97] outline recommendations for older adults who present with the falls syndrome. Patients with osteoporosis may benefit greatly from a multifactorial risk assessment for falls if they present with more than 2 falls per year, or if a fall leads to an injury or is the chief complaint in the clinical visit. The endocrinologist should ask about falls, and refer the patient to a geriatrician or to a falls clinic. Prevention of falls plays a major role in the prevention of morbidity in patients with osteoporosis. The CDC Stopping Elderly Accidents, Deaths & Injuries (STEADI) program offers tools for assessment and prevention of falls (available at http://www.cdc.gov/steadi/) [98]. Furthermore, for patients at high risk for falls, home safety assessment and modification in those with a previous fall can reduce the rate of falls and risk for falling [99].

Regarding secondary prevention, it is important to recognize patient characteristics that are associated with greater risk for a subsequent fall. A recent systematic review and meta-analysis found that female, institutionalization, decreased vision, dizziness, dementia, cardiac and respiratory diseases, in addition to osteoporosis, increased the risk for a second contralateral hip fracture [100]. Special attention ought to be placed for secondary prevention in those cases.

22.6.4 Problems with Calcium Metabolism

The incidence and prevalence of primary hyperparathyroidism (PHP) is greater with aging. Similarly, the prevalence of cancer associated with non-parathyroid hormone dependent hypercalcemia also increases with aging. For PHP, advanced age is not a contraindication for parathyroidectomy; however, assessments of function, cognition, life-expectancy, and other age-related conditions are needed to complete the assessment and recommendation towards surgery, or chronic medical management with a calcimimetic (Cinacalcet) [101], as well as the pertinent interventions for diagnosis and management of secondary osteoporosis, falls and fracture prevention.

Older adults are a heterogeneous population with a range of comorbidities that influence treatment in all illnesses including calcium disorders. If 10 years passes and PHP is found in Mr. F. (Case 1) who is now 88 years old, with well-controlled diabetes, and preserved physical and cognitive function, parathyroidectomy will be the procedure of choice. However, for Mrs. B. (Case 4), now 82 years old, with cardiovascular disease, severe heart failure, advanced dementia

and poor physical function, parathyroidectomy may not be applicable, and medical management may be the first option to discuss with her family.

22.7 Thyroid Disorders

Thyroid disorders are common in older adults with clinical presentations that include both long-standing and new-onset illnesses. Clinical and subclinical hypothyroidism and hyperthyroidism are common as thyroid nodular disease and differentiated thyroid cancer (DTC).

22.7.1 Hypothyroidism

The incidence of hypothyroidism (defined as high TSH and low T-4) increases with age as a result of long-standing hypothyroid disease, resulting from the treatment for hyperthyroidism and differentiated thyroid cancer (DTC), or as a side effect of amiodarone therapy. Diagnosis of hypothyroidism can be delayed by comorbidities, including depression and cognitive decline, thus proper screening must be implemented.

Thyroid hormone replacement with levothyroxine (LT4) is usually based on lean body mass (~1.6 mcg per kg-weight) for healthy middle age patients [99]; age-related loss of lean body mass [103] often means dose adjustments are needed with increasing age. In addition, lower starting dosages (25–50 mcg per day) is recommended for healthy older adults, lower (12.5–25 mcg per day) for those with known or possible cardiovascular disease. Replacement therapy must strive to avoid overtreatment, with careful monitoring every 4–6 weeks, and dose adjustments of 12.5 mcg, until TSH target is reached. A start and go slow approach may also provide more stable TSH values over time [102, 104, 105].

For a patient with a clinical presentation similar to Mr. F. (Case 1), who is otherwise healthy and recently developed primary hypothyroidism, LT4 therapy could reach a full dose replacement similar to a younger person. In contrast, for a patient similar to Mrs. B. (Case 4), a more careful approach is required, given concerns for bone and cardiovascular risk.

Guidelines recommend TSH targets between 1 and 2.5 mIU/L, but normal age-specific TSH values are higher in older adults when compared with younger people [106]. The NHANES study has shown that the 97.5 centiles for TSH in the 20- to 29-year and the 80-year and older groups were 3.56 and 7.49 mIU/L, respectively and 70 % of older patients with TSH greater than 4.5 mIU/L were within their age-specific reference range. In addition, some suggest that higher TSH values in healthy older individuals might be associated with better cognitive and physical function [107, 108].

While there are no randomized controlled trials, we recommend caution when treating hypothyroidism in older adults, especially in the oldest old. A TSH closer to 2.5 mIU/L, and perhaps higher (within the normal range) may be more appropriate, whereas reaching TSH of 1 mIU/L may be potentially harmful.

In addition, for older adults with hypothyroidism related to Hashimoto's thyroiditis, it is important to be aware of the risk of autoimmune atrophic gastritis [109], given potential clinical implications for nutrition and pharmacologic therapies.

22.7.2 Subclinical Hypothyroidism

This condition is defined as a high TSH and normal T-4. The European Thyroid Association provides guidelines for subclinical hypothyroidism management [110] with two potential scenarios: the first one with TSH values range between the upper limit of normal and 10 mIU/L, and the second when TSH is greater than 10 mIU/L. About 90 % of cases fall in the first scenario [111] and have milder clinical consequences [112, 113].

Guidelines recommend careful monitoring and a watchful waiting in the oldest old [9], avoiding a rush to diagnosis based on one value and rather rechecking TSH at 3–6 months intervals.

A recent systematic-review assessed the risk of stroke in those with subclinical hypothyroidism [114]. Compared to those with normal thyroid function, no increased risks were found in individuals with subclinical hypothyroidism in those aged 65 and older. A subsequent analysis from this research group suggested a pattern of increased risk for fatal stroke in younger individuals with higher TSH concentrations [115].

Increased risk for depression has been reported in subjects older than 60 years with untreated subclinical hypothyroidism [116], while a more recent prospective study in adults age 70–82 [117] did not show an association of subclinical hypothyroidism with increased depressive symptoms among those at high cardiovascular risk.

Regarding cognitive decline, a recently published meta-analysis [118] found no association between subclinical hypothyroidism and cognitive performance (impaired mini-mental state examination, executive function, and memory).

Regarding quality of life, a small randomized trial compared the impact of thyroid hormone replacement versus placebo in adults who screened positive for hypothyroidism and those with subclinical hypothyroidism. They found improved quality of life (less tiredness) for the hypothyroid [119] but not those with subclinical hypothyroidism. Therefore, clinical judgment is crucial in the management of subclinical hypothyroidism in older adults. Caution with over-screening

leading to overtreatment has been raised, particularly if age-adjusted normal limits of TSH are not used [120]. Decisions should include a specific evaluation of the pre-existent cardiovascular risk, degree of TSH elevation, comorbidity, and frailty [107].

22.7.3 Hyperthyroidism

Excess thyroid hormone may have major impact on bone and cardiovascular health in older adults [121]. Graves' disease is the most common cause of hyperthyroidism, while toxic multinodular goiter and toxic adenoma are more prevalent in iodine deficiency regions [122], and have a faster progression to hypothyroidism post-treatment [123].

Any abnormality in thyroid function can present with non-specific symptoms. For example, apathetic hyperthyroidism in seniors classically has none of the typical symptoms of younger onset hyperthyroidism such as heat intolerance, tremor, nervousness, tachycardia, and others [124], and rather presents with cardiovascular features (atrial fibrillation), depression, lethargy, weakness, weight loss, and without goiter or ocular manifestations [125]. In general, anorexia and atrial fibrillation are more frequent in older than in younger patients [126]. Furthermore, the greater prevalence of HTN and cardiovascular disease in this age group may lead to chronic use of beta-blockers, which mask hyperadrenergic symptoms [124].

Radioactive iodine (RAI) is the preferred therapeutic approach, based on better success rate and safety profile with lesser risk for recurrence. Thionamides become second line alternative therapy, and consideration should be given to the risk-benefit, due to potential adverse reactions, medication interaction, and the greater prevalence of liver and bone marrow diseases in this age group.

22.7.4 Subclinical Hyperthyroidism

Regarding subclinical hyperthyroidism, two scenarios have been described: the first one with TSH between 0.1 mIU/L and the lower limit of normal (grade 1), and the second with TSH below 0.1 mIU/L (grade 2). There is greater concern in grade 2 for cardiovascular risk (heart dysfunction, coronary heart disease, and atrial fibrillation), osteoporosis, and progression to overt hyperthyroidism. Therefore, both American and European guidelines recommend treatment for grade 2 subclinical hyperthyroidism [121, 127]. Nonetheless, persistently suppressed TSH in the grade 1 range may need treatment in older adults given the increased risk for atrial fibrillation and heart failure.

A recent analysis from the Rotterdam Study examined the association between increased thyroid hormone levels and risks for atrial fibrillation [128]. Among subjects with normal free T4 (FT4) levels, higher risks for atrial fibrillation were found in those with FT4 levels in the highest quartile when compared to those in the lowest quartile. The absolute 10-year risk was greater in subjects older than 65 compared to younger subjects.

22.7.5 Differentiated Thyroid Cancer

Late-onset DTC typically presents in older patients and has unique recurrence features, an atypical TNM model, different responses to total thyroidectomy, and a different survival [129]. The older the age the greater the risk for more advanced stage at presentation and the greater the risk for recurrence.

Older adults undergoing TSH suppression with thyroid hormone replacement, post-thyroidectomy for DTC, may be at greater risk of adverse events (e.g., atrial fibrillation and osteoporosis) compared to younger individuals [130, 131]. Potential benefits with beta blockers for prophylaxis have been suggested but more research is needed [132]. Current management guidelines also suggest therapy for osteoporosis [125] and recommendations to preserve bone health such as exercise and supplementation with calcium and vitamin D.

22.8 Hypogonadism

The endocrine evaluation of older men should include evaluation of their gonadal function. Most symptoms associated with gonadal dysfunction are non-specific but may impact quality of life and wellbeing.

22.8.1 Clinical Diagnosis

There is significant heterogeneity in the way older men with hypogonadism present clinically. For men with early-onset hypogonadism due primary to testicular failure or secondary to pituitary tumor resection, long-term monitoring and management is required. Many of the symptoms of testosterone deficiency of late onset (i.e., erectile dysfunction, depression, decreased energy, weakness) may also occur in age-related comorbidities (diabetes, cardiovascular disease, depression, frailty syndrome) and will not improve with testosterone replacement alone. Thus, counseling about expectations from evaluation and treatment for hypogonadism is advised [133, 134].

Since the diagnosis of late-onset hypogonadism often is challenging, a European study evaluated the clinical and hormonal profile in middle-age and older men [129]. Sexual symptoms (poor morning erection, low sexual desire, and

erectile dysfunction) were significantly related to low testosterone levels. Less specific symptoms such as depression and fatigue were more typically related to co-existing conditions and had greater impact in quality of life and ability for self-care [136–138]. This fact makes the clinical monitoring of patients on replacement testosterone difficult.

22.8.2 Laboratory Assessment

It is important to recognize that chronic diseases may impact hormonal values [139]. Obesity was associated with lower testosterone values in the Massachusetts Male Aging Study and the European Male Aging Study [140, 141]. Diabetes and heart failure have also been associated with hypogonadism [142, 143]. These diseases are associated with fatigue, poor sleep, insomnia, and other non-specific symptom, which may lead to impaired metabolism, obesity, and impaired gonadal function. In addition, older patients may require medications (opioids, glucocorticoids, and spironolactone) which decrease testosterone levels [144]. Thus, after thorough discussion with patients, laboratory screening for hypogonadism can be considered in older adults with symptoms of hypogonadism [133, 134].

There are changes in the circadian rhythm for testosterone, so blood sample collection is recommended early in the morning after a good night's rest and tested using reliable assays; low levels should be confirmed with a second morning sample. An older person with insomnia or sleep disorders may have inaccurate levels. Consider assessment of free testosterone in the setting of abnormal sex hormone binding globulin, especially in older men with total testosterone concentrations near the lower limit of the normal range and in whom alterations of sex-hormone binding globulin are suspected [134].

Late-onset hypogonadism develops in a relative small percentage of all older men (2.1 % in the European Male Aging Study) [145]. Those with testosterone levels well below the lower limit of 300 ng/dl, i.e. values below 150 ng/dl [146] ought to be reassed (diagnosis requires confirmation in separate occassions). Then, further informed discussion for treatment should follow if results are consistently low in the setting of syndromal presentation (low values alone do not justify treatment). Moreover, it is important to consider potential risks affecting those in whom therapy may be clinically indicated.

22.8.3 Adverse Effects of Testosterone Replacement Therapy

There is growing concern with the increase in testosterone prescriptions and potential health consequences [147]. The American Association of Clinical Endocrinologists recently addressed potential cardiovascular risk [148] and concluded that there is no compelling evidence that testosterone therapy either increases or decreases cardiovascular risk but stated that treatment in older adults should be extra cautious.

Controversy related to cardiovascular safety of testosterone supplementation continues among experts. Several authors have stated the need for adequate randomized trials, powered to assess the impact of testosterone on cardiovascular health and outcomes in the older population [149]. Until then, the decision to treat hypogonadism in older adults must be based on a clinical approach considering the patient's health status, physical and cognitive function, and incorporating the patients' goals, risks, and any special considerations [150].

For those cases in whom testosterone treatment clearly offer greater benefits than risks, recommended monitoring includes surveillance for erythrocytosis, hypertension, prostate disease, and liver abnormalities [151].

22.8.4 Testosterone Replacement Therapy

When treatment is warranted, replacement should aim for testosterone levels in the mid-normal range [146, 151], with suggested target around 400 ng/dl for older men, which is less than in younger individuals.

Building on the clinical scenarios of the learning cases:

If an otherwise healthy older adult, like Mr. F. (Case 1), returns to the clinic for a yearly follow-up, and reports decreased libido, and erectile dysfunction, his symptoms may be due to hypogonadism, and require evaluation. Assuming the laboratory assessments confirm low testosterone values, e.g. 180, and 140 ng/dL, with corresponding increased gonadotropins, the diagnosis of testicular hypogonadism is established and it will be appropriate to discuss testosterone replacement. For this relatively healthy older man, with preserved physical function, cognition and good social support, treatment can improve symptoms and his quality of life.

However, there will be more complex scenarios. For example, a 70-year-old man who has diabetes, coronary artery disease, and a known family history of prostate cancer, presents with complaints of fatigue, depression, and inability to perform vigorous activity. Laboratory assessment shows borderline low testosterone values of 290 and 280 ng/dL. Given the family history of prostate cancer and the potential concerns about cardiovascular safety, testosterone therapy may not be initially recommended. These non-specific symptoms could be explained by stress, poor sleep, and impaired physical function. Furthermore, the risk benefit ratio of testosterone replacement is not clearly favorable. On the other hand, a healthy, functional, and cognitively intact

68-year-old man with hypertension and family history (cousin) of prostate cancer is found to have osteoporosis, and unequivocally low testosterone values (e.g., 150 and 140 ng/dL), and a normal prostate specific antigen. In this case, testosterone replacement will improve bone health, quality of life, function, and future outcomes, since a fracture could be devastating to him.

References

1. American Diabetes Association. Fast facts data and statistics about diabetes. March, 2015. Available at http://professional.diabetes.org/admin/UserFiles/0%20-%20Sean/14_fast_facts_june2014_final3.pdf. Accessed 8 Oct 2015.
2. Centers for Disease Prevention and Control. Incidence of diagnosed diabetes per 1,000 population aged 18-79 years, by age, United States, 1980-2014. Available at http://www.cdc.gov/diabetes/statistics/incidence/fig3.htm. Accessed 8 Oct 2015.
3. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2014. Available at http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf. Accessed 8 Oct 2015.
4. Centers for Disease Control and Prevention. National Diabetes Statistics Report: estimates of diabetes and its burden in the United States, 2014. Atlanta, GA: US Department of Health and Human Services; 2014. Available at http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf. Accessed 8 Oct 2015.
5. Kirkman SM, Briscoe VJ, Clark N, et al. Diabetes in older adults. Diabetes Care. 2012;35:2650–64.
6. American Diabetes Association. Older adults. Sec 10. In standards of Medical care in Diabetes – 2015. Diabetes Care 2015;38(Suppl 1):S67–S9.
7. Valencia WM, Florez H. Pharmacological treatment of diabetes in older people. Diabetes Obes Metab. 2014;16(12):1192–203.
8. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015;38:140–9.
9. American Geriatrics Society. Guiding principles for the care of older adults with multimorbidity: an approach for clinicians. American Geriatrics Society Expert Panel on the care of older adults with multimorbidity. J Am Geriatr Soc. 2012;60(10):E1–E25.
10. Huang ES, Laiteerapong N, Liu JY, et al. Rates of complications and mortality in older patients with diabetes mellitus. The diabetes and aging study. JAMA Inter Med. 2014;174(2):251–8.
11. Strotmeyer ES. Diabetes and aging. Clin Geriatr Med 2015;31(1):xiii–xvi.
12. American Diabetes Association. Initial evaluation and diabetes management planning. Sec 3. In standards of Medical care in Diabetes – 2015. Diabetes Care 2015;38(Suppl 1):S17–S9.
13. Sinclair A, Morley JE, Rodriguez-Manas L, et al. Diabetes mellitus in older people: position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for older people (EDWPOP), and the International Task Force of Experts in Diabetes. J Am Med Dir Assoc. 2012;13:497–502.
14. Lin J, Zhou S, Wei W, Pan C, Lingohr-Smith M, Levin P. Does clinical inertia vary by personalized A1c goal? A study of predictors and prevalence of clinical inertia in a US managed care setting. Endocr Pract. 2015. [Epub ahead of print].
15. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393–403.
16. Diabetes Prevention Program Research Group, Crandall J, Schade D, et al. The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. J Gerontol A Biol Sci Med Sci. 2006;61(1):1075–81.
17. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE/ACE comprehensive diabetes management algorithm 2015. Endocr Pract. 2015;21(4):438–47.
18. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;368(24):2545–59.
19. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560–72.
20. Duckworth WC, Abraira C, Moritz T, et al. Glucose control and vascular complications in Veterans with type 2 diabetes. N Eng J Med. 2009;360:129–39.
21. American Geriatrics Society Expert Panel on the Care of Older Adults with Diabetes Mellitus. Guidelines abstracted from the American Geriatrics Society guidelines for improving the care of older adults with diabetes mellitus: 2013 Update. J Am Geriatr Soc. 2013;61:2020–26
22. The American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63:2227–46.
23. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research and policy implications of a core geriatric concept. J Am Geriatr Soc. 2007;55(5):780–91.
24. Munshi M. Managing the "geriatric syndrome" in patients with type 2 diabetes. Consult Pharm. 2008;23(Suppl B):12–6.
25. Boyd CM, Darer J, Boult C, et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA. 2005;294(60):716–24.
26. Peron EP, Ogbonna KC, Donohoe KL. Antidiabetic medications and polypharmacy. Clin Geriatr Med. 2015;31:17–27.
27. Wu Q, Tchetgen Tchetgen EJ, Qsypuk T, et al. Estimating the cognitive effects of prevalent diabetes, recent onset diabetes, and the duration of diabetes among older adults. Dement Geriatr Cogn Disord. 2015;39:239–49.
28. Bangen KJ, Gu Y, Gross AL, et al. Relationship between type 2 diabetes mellitus and cognitive change in a multiethnic elderly cohort. J Am Geriatr Soc. 2015;63:1075–83.
29. Rawlings AM, Sharrett AR, Schneider ALC, et al. Diabetes in midlife and cognitive change over 20 years. A cohort study. Ann Intern Med. 2014;161:785–93.
30. Feinkohl I, Aung PP, Keller M, et al. Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the Edinburg type 2 diabetes study. Diabetes Care. 2014;37:507–15.
31. Launer LJ, Miller ME, Williamson JD, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomized open-label substudy. Lancet Neurol. 2011;10:969–77.
32. Espeland MA, Rapp SR, Bray GA, et al. Long-term impact of behavioral weight loss intervention on cognitive function. J Gerontol A Biol Sci Med Sci. 2014;69(9):1101–8.
33. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CPJ, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes. JAMA. 2009;301:1565–72.
34. Punthakee Z, Miller ME, Launer LE, et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes. Diabetes Care. 2012;35:787–93.

35. CDC overweight and obesity facts. Centers for Disease Control and Prevention. 2014. Available at. http://www.cdc.gov/obesity/data/adult.html. Accessed 8 Oct 2015.
36. Valencia WM, Stoutenberg M, Florez H. Weight loss and physical activity for disease prevention in obese older adults: an important role for lifestyle management. Curr Diab Rep. 2014;14:539–48.
37. Loef M, Walach H. Midlife obesity and dementia: meta-analysis and adjusted forecast of dementia prevalence in the United States and China. Obesity. 2013;21:E51–5.
38. WHO Global strategy on diet, physical activity and health. Obesity and overweight facts. World Health Organization. 2003. Available at http://www.who.int/dietphysicalactivity/media/en/gsfs_obesity.pdf. Accessed 8 Oct 2015.
39. The Obesity Society. Obesity, bias and stigmatization. Available at http://www.obesity.org/resources/facts-about-obesity/bias-stigmatization. Accessed 8 Oct 2015.
40. Carnethon MR, De Chavez PJD, Biggs ML, et al. Association of weight status with mortality in adults with incident diabetes. JAMA. 2012;308:581–90.
41. Lavie CJ, McAuley PA, Church TS, Milani RV, Blair SN. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. J Am Coll Cardiol. 2014;63:1345–54.
42. Hainer V, Aldhoon-Hainerová I. Obesity paradox does exist. Diabetes Care. 2013;36 Suppl 2:S276–81.
43. McAuley PA, Beavers KM. Contribution of cardiorespiratory fitness to the obesity paradox. Prog Cardiovasc Dis. 2014;56:434–40.
44. Barry VW, Baruth M, Beets MW, Durstine JL, Liu J, Blair SN. Fitness vs fatness on all-cause mortality: a meta-analysis. Prog Cardiovasc Dis. 2014;56:382–90.
45. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet. 1999;353(9156):878–82.
46. Kannegaard PN, van derMark S, Eiken P, Abrahamsen B. Excess mortality in men compared with women following a hip fracture. National analysis of comedications, comorbidity and survival. Age Ageing. 2010;39(2):203–9.
47. Rizzoli R, Branco J, Brandi ML, et al. Management of osteoporosis in the oldest old. Osteoporos Int. 2014;25:2507–29.
48. Chevalley T, Guilley E, Hermann FR, Hoffmeyer P, Rapin CH, Rizzoli R. Incidence of hip fracture over a 10-year period (1991-2000): reversal of a secular trend. Bone. 2007;40:1284–9.
49. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int. 2006;17:1726–33.
50. Watts NB, Bilezikian JP, Camacho PM, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of postmenopausal osteoporosis. Endocr Pract. 2010;16 Suppl 3:1–37.
51. U.S. Preventive Services Task Force. Screening for osteoporosis: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2011;154:356–64.
52. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(6):1802–22.
53. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25:2359–81.
54. Burge R, Dawson-Hughers B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007;22:465–75.
55. Office of the Surgeon General. Rockville (MD). Bone health and osteoporosis: a report of the surgeon general. Available on line at http://www.ncbi.nlm.nih.gov/books/NBK45502/#ch5.s8; 2004.
56. Bouxsein ML, Genant HK, International Osteoporosis Foundation. The breaking spine. Available at http://www.iofbonehealth.org/sites/default/files/PDFs/WOD%20Reports/2010_the_breaking_spine_en.pdf. Accessed 16 Nov 2015.
57. Goldstein CL, Chutkan NB, Choma TJ, Orr RD. Management of the elderly with vertebral compression fractures. Neurosurgery. 2015;77:533–45.
58. International Osteoporosis Foundation (IOF). Impact of osteoporosis. Available online at http://www.iofbonehealth.org/impact-osteoporosis. Accessed 23 Oct 2015.
59. Darba J, Kaskens L, Perez-Alvarez N, Palacios S, Neyro JL, Rejas J. Disability-adjusted-life-years losses in postmenopausal women with osteoporosis: a burden of illness study. BMC Public Health. 2015;15:234–43.
60. Stenderup K, Justesen J, Clausen C, Kassem M. Aging is associated with decreased maximal life span and accelerated senescence of bone marrow stromal cells. Bone. 2003;33:919–26.
61. Zhou S, Greenberger JS, Epperly MW, et al. Age-related intrinsic changes in human bone-marrow-derived mesenchymal stem cells and their differentiation to osteoblasts. Aging Cell. 2008;7:335–43.
62. D'Amelio P, Roato I, D'Amico L, et al. Bone and bone marrow pro-osteoclastogenic cytokines are upregulated in osteoporosis fragility fractures. Osteoporos Int. 2011;22:2869–77.
63. Kanis JA, Oden A, McCloskey EV, Johansson H, Wahl DA, Cooper C, on behalf of the IOF Working Group on Epidemiology and Quality of Life. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int. 2012;23:2239–56.
64. Kanis JA, Johansson H, Oden A, Dawson-Hughes B, Melton 3rd LJ, McCloskey EV. The effects of a FRAX revision for the USA. Osteoporos Int. 2010;21(1):35–40.
65. Donaldson MG, Cawton PM, Lui LY, et al. Estimates of the proportion of older white men who would be recommended for pharmacologic treatment by the new US National Osteoporosis Foundation guidelines. J Bone Miner Res. 2010;25:1506–11.
66. Watts NB. Osteoporosis in men. Endocr Pract. 2013;19:834–8.
67. Laurent M, Gielen E, Claessens F, Boonen S, Vanderschueren D. Osteoporosis in older men: recent advances in pathophysiology and treatment. Best Pract Res Clin Endocrinol Metab. 2013;27(4):527–39.
68. Sayer AA, Robinson SM, Patel HP, Shavlakadze T, Cooper C, Grounds MD. New horizons in the pathogenesis, diagnosis and management of sarcopenia. Age Ageing. 2013;42:145–50.
69. Di Monaco M, Castiglione C, Vallero F, Di Monaco R, Tappero R. Sarcopenia is more prevalent in men than in women after hip fracture: a cross-sectional study of 591 inpatients. Arch Gerontol Geriatr. 2012;55:e48–52.
70. Bijlsma AY, Meskers CG, Westendorp RG, Maier AB. Chronology of age-related disease definitions: osteoporosis and sarcopenia. Ageing Res Rev. 2012;11(2):320–4.
71. Gibson MJ, Andres RO, Isaacs B, Radebaugh T, Worm-Petersen J. The prevention of falls in later life. A report of the Kellogg International Work Group on the prevention of falls by the elderly. Dan Med Bull. 1987;34 Suppl 4:1–24.
72. Centers for Disease Control and Prevention. Important facts about falls. Available at http://www.cdc.gov/homeandrecreationalsafety/falls/adultfalls.html. Accessed 16 Nov 2016.
73. Hayes WC, Myers ER, Morris JN, Gerhart TN, Yett HS, Lipsitz LA. Impact near the hip dominates fracture risk in elderly nursing home residents who fall. Calcif Tissue Int. 1993;52:192–8.
74. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–56.
75. Klotzbuecher CM, Ross PD, Landsman PB, et al. Patients with prior fractures have an increased risk of future fractures: a sum-

mary of the literature and statistical synthesis. J Bone Miner Res. 2000;15:721–39.
76. Lonnroos E, Kautiainen H, Karppi P, et al. Incidence of second hip fractures. A population-based study. Osteoporos Int. 2007;18:1279–85.
77. Berry SD, Samelson EJ, Hannan MT, et al. Second hip fracture in older men and women: the Framingham Study. Arch Intern Med. 2007;167:1971–6.
78. Shen S-H, Huang K-C, Tsai Y-H, et al. Risk analysis for second hip fracture in patients after hip fracture surgery: a nationwide population-based study. J Am Med Dir Assoc. 2014;2015:725–31.
79. Toussaint ND, Elder GJ, Kerr PG. Bisphosphonates in chronic kidney disease; balancing potential benefits and adverse effects on bone and soft tissue. Clin J Am Soc Nephrol. 2009;4(1):221–33.
80. Miller PD. The kidney and bisphosphonates. Bone. 2011;49(1): 77–81.
81. Batchelor P. The changing epidemiology of oral diseases in the elderly, their growing importance for care and how they can be managed. Age Aging. 2015;44:1064–70.
82. Spanou A, Lyritis GP, Chronopoulos E, Tournis S. Management of bisphosphonate-related osteonecrosis of the jaw: a literature review. Oral Dis. 2015;21(8):927–36.
83. Body JJ, Bergmann P, Boonen S, et al. Non-pharmacological management of osteoporosis: a consensus of the Belgian Bone Club. Osteoporos Int. 2011;22:2769–88.
84. Diab DL, Watts NB. Diagnosis and treatment of osteoporosis in older adults. Endocrinol Metab Clin N Am. 2013;42:305–17.
85. Verbrugge FH, Gielen E, Milisen K, Boonen S. Who should receive calcium and vitamin D supplementation? Age Ageing. 2012;41:576–80.
86. Sipponen P, Maaross HI. Chronic gastritis. Scand J Gastroenterol. 2015;50(6):657–67.
87. Mayo Clinic. Healthy Lifestyle. Nutrition and healthy aging. Available at http://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/calcium-supplements/art-20047097?pg=2. Accessed 31 Dec 2015.
88. Black LJ, Anderson D, Clarke MW, Ponsonby A-L, Lucas RM, Ausimmune Investigator Group. Analytical bias in the measurement of serum 25-hydroxyvitamin D concentrations impairs assessment of vitamin D status in clinical and research settings. PLoS One. 2015;10:1–14.
89. Gallagher JC. Vitamin D, and aging. Endocrinol Metab Clin N Am. 2013;42:319–32.
90. Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. J Clin Endocrinol Metab. 2004;89(11):5387–91.
91. Bjelakovic G, Gluud LL. Nikolova, et al. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev. 2014;10(1), CD007470.
92. Sherrington C, Whitney JC, Lord SR, Herbert RD, Cumming RG, Close JC. Effective exercise for the prevention of falls: a systematic review and meta-analysis. J Am Geriatr Soc. 2008;56(12): 2234–43.
93. Choi M, Hector M. Effectiveness of intervention programs in preventing falls: a systematic review of recent 10 years and meta-analysis. J Am Med Dir Assoc. 2012;13(2):188.e13–188.e21
94. Lee MS, Pittler MH, Shin BC, Ernst E. Tai Chi for osteoporosis: a systematic review. Osteoporos Int. 2008;19:139–46.
95. Go4Life from the National Institute on Aging at NIH. Available at https://go4life.nia.nih.gov/. Accessed 14 Dec 2015.
96. National Council on Aging. Exercise programs that promote senior fitness. Available at https://www.ncoa.org/center-for-healthy-aging/physical-activity/physical-activity-programs-for-older-adults/. Accessed 14 Dec 2015.
97. American Geriatrics Society and British Geriatrics Society. Summary of the updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc. 2011;59:148–57.
98. Centers for Disease Control and Prevention. STEADI stopping elderly accidents, deaths and injuries. Available at http://www.cdc.gov/steadi/. Accessed 14 Dec 2015.
99. Gillispie LD, Robertson MC, Gillispie WJ, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2012;12(9), CD007146.
100. Liu S, Zhu Y, Chen W, Sun T, Cheng J, Zhang Y. Risk factors for the second contralateral hip fracture in elderly patients: a systematic review and meta-analysis. Clin Rehabil. 2015;29(3): 285–94.
101. Marcocci C, Bollerslev J, Khan AA, Shoback DM. Medical management of primary hyperparathyroidism: proceedings of the fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. J Clin Endocrinol Metab. 2014;99(10):3607–18.
102. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement. Thyroid. 2014;24(12):1670–751.
103. Cunningham JJ, Barzel US. Lean body mass is a predictor of the daily requirement for thyroid hormone in older men and women. J Am Geriatr Soc. 1984;32:204–7.
104. Kabadi UM. Variability of L-thyroxine replacement dose in elderly patients with primary hypothyroidism. J Fam Pract. 1987;24:473–7.
105. Pecina J, Garrison GM, Bernard M. Levothyroxine dosage is associated with stability of TSH values. Am J Med. 2014;127:240–5.
106. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab. 2007;92:4575–82.
107. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frolich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. JAMA. 2004;292:2591–9.
108. Simonsick EM, Newman AB, Ferrucci L, et al. Subclinical hypothyroidism and functional mobility in older adults. Arch Intern Med. 2009;169:2011–7.
109. Centanni M, Marignani M, Gargano L, et al. Atrophic body gastritis in patients with autoimmune thyroid disease: an underdiagnosed association. Arch Intern Med. 1999;159:1726–30.
110. Pearce SHS, Brabant G, Duntas LH, et al. 2013 ETA guideline: management of subclinical hypothyroidism. Eur Thyroid J. 2013;2:215–28.
111. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87:489–99.
112. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004;29:228–38.
113. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160: 526–34.
114. Chaker L, Baumgartner C, Ikram MA, et al. Subclinical thyroid dysfunction and the risk of stroke: a systematic review and meta-analysis. Eur J Epidemiol. 2014;29:791–800.
115. Chaker L, Baumgartner C, den Elzen WPJ, et al. Subclinical hypothyroidism and the risk of stroke events and fatal stroke: an individual participant data analysis. J Clin Endocrinol Metab. 2015;100:2181–91.
116. Chueire VB, Romaldini JH, Ward LS. Subclinical hypothyroidism increases the risk for depression in the elderly. Arch Gerontol Geriatr. 2007;44(1):21–8.

117. Blum MR, Bauer DC, Collet T-H, et al. Subclinical thyroid dysfunction and fracture risk. A meta-analysis. JAMA. 2015;313(20): 2055–65.
118. Akintola AA, Jansen SW, van Bodegom D, et al. Subclinical hypothyroidism and cognitive function in people over 60 years: a systematic review and meta-analysis. Front Aging Neurosci. 2015;7(150):1–10.
119. Abu-Helalah M, Law MR, Bestwick JP, Monson JP, Wald NJ. A randomized double-blind crossover trial to investigate the efficacy of screening for adult hypothyroidism. J Med Screen. 2010;17: 164–9.
120. Hennessey JV, Espaillat R. Diagnosis and management of subclinical hypothyroidism in elderly adults: a review of the literature. J Am Geriatr Soc. 2015;63:1663–73.
121. Bahn RS, Burch HB, Cooper DS, et al. American Thyroid Association/American Association of Clinical Endocrinologists. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid. 2011;21(6): 593–687.
122. Laurberg P, Pedersen KM, Vestergaard H, Sigurdsson G. High incidence of multinodular toxic goitre in the elderly population in a low iodine intake area vs. high incidence of Graves' disease in the young in a high iodine intake area: comparative surveys of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland. J Intern Med. 1991;229:415–20.
123. Ceccarelli C, Bencivelli W, Vitti P, Grasso L, Pinchera A. Outcome of radioiodine-131 therapy in hyperfunctioning thyroid nodules: a 20 years' retrospective study. Clin Endocrinol (Oxf). 2005;62:331–5.
124. Mitrou P, Raptis SA, Dmitriadis G. Thyroid disease in older people. Maturitas. 2011;70:5–9.
125. Wu W, Sun Z, Yu J, et al. A clinical retrospective analysis of factors associated with apathetic hyperthyroidism. Pathobiology. 2010;77:46–51.
126. Trivalle C, Doucet J, Chassagne P, et al. Differences in the signs and symptoms of hyperthyroidism in older and younger patients. J Am Geriatr Soc. 1996;46:50–3.
127. Biondi B, Bartalena L, Cooper D, Hegedus L, Laurberg P, Kahaly G. The 2015 European Thyroid Association Guidelines on diagnosis and treatment of endogenous subclinical hyperthyroidism. Eur Thyroid J. 2015;4:149–63.
128. Chaker L, Heeringa J, Dehghan A, et al. Normal thyroid function and the risk of atrial fibrillation: the Rotterdam study. J Clin Endocrinol Metab. 2015;100:3718–24.
129. Alexander EK, Bible KC, Doherty GM, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26:1–133.
130. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med. 1994;331:1249–52.
131. Flynn RW, Bonellie SR, Jung RT, MacDonald TM, Morris AD, Leese GP. Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. J Clin Endocrinol Metab. 2010;95:186–93.
132. Taillard V, Sardinoux M, Oudot C, et al. Early detection of isolated left ventricular diastolic dysfunction in highrisk differentiated thyroid carcinoma patients on TSH-suppressive therapy. Clin Endocrinol (Oxf). 2011;75:709–14.
133. Petak SM, Nankin HR, Spark RF, Swerdloff RS, Rodriguez-Riqau LJ. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients – 2002 update. Endocr Pract. 2002;8:440–59.
134. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95:2536–59.
135. Wu FC, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010;363:123–35.
136. Gielissen MF, Knoop H, Servaes P, et al. Differences in the experience of fatigue in patients and healthy controls: patients' descriptions. Health Qual Life Outcomes. 2007;5:36–42.
137. Park M, Reynolds III CF. Depression among older adults with diabetes. Clin Geriatr Med. 2015;31:117–37.
138. Ginsberg TB. Male sexuality. Clin Geriatr Med. 2010;26: 185–95.
139. Travison TG, Araujo AB, Kupelian V, et al. The relative contributions of aging, health, and lifestyle factors to serum testosterone decline in men. J Clin Endocrinol Metab. 2007;92:549–55.
140. Mohr BA, Bhasin S, Link CL, O'Donnell AB, McKinlay JB. The effect of changes in adiposity on testosterone levels in older men: longitudinal results from the Massachusetts Male Aging Study. Eur J Endocrinol. 2006;155:443–52.
141. Wu FC, Tajar A, Pye SR, et al. Hypothalamic-pituitary-testicular axis dysruptions in older men are differentially linked to age and modifiable risk factors: the European male aging study. J Clin Endocrinol Metab. 2008;93:2737–45.
142. Dandona P, Dhindsa S. Hypogonadotropic hypogonadism in type 2 diabetes and obesity. J Clin Endocrinol Metab. 2011;96: 2643–51.
143. Jankowska EA, Biel B, Majda J, et al. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. Circulation. 2006;114:1829–37.
144. Basaria S. Reproductive aging in men. Endocrinol Metab Clin N Am. 2013;42:255–70.
145. Tajar A, Huhtaniemi IT, O'Neil TW, et al. Characteristics of androgen deficiency in late-onset hypogonadism: results from the European Male Aging Study (EMAS). J Clin Endocrinol Metab. 2012;97:1508–16.
146. Feldman HA, Loncope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab. 2002;87:589–98.
147. Gan EH, Pattman S, Pearce S, Quinton R. Many men are receiving unnecessary testosterone prescriptions. BMJ. 2012;345, e5469.
148. Goodman N, Guay A, Dandona P, et al. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the association of testosterone and cardiovascular risk. Endocr Pract. 2015;21:1066–73.
149. Gencer B, Mach F. Testosterone: a hormone preventing cardiovascular disease or a therapy increasing cardiovascular events? Eur Heart J. 2015; pii: ehv439. [Epub ahead of print].
150. Matsumoto AM. Testosterone administration in older men. Endocrinol Metab Clin N Am. 2013;43:271–86.
151. Bhattacharya RK, Bhattacharya SB. Late-onset hypogonadism and testosterone replacement in older men. Clin Geriatr Med. 2015;31:631–44.